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REGENERATIVE CAPACITY OF VENTRAL ROOTS AFTER AVULSION FROM THE SPINAL CORD

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BALTIMORE

The object of this paper is to prove unfounded the prevailing assumption that ventral nerve roots cannot regenerate if avulsed from the spinal cord. That they do not regenerate in man is general clinical experience, certainly. Yet in exploring to their limits the regenerative capacities of various parts of the nervous system, one may find that clinical experience is a too conservative guide. One would like to know whether the failure to regenerate is primarily one of the nerve tissue or is secondarily due to obstacles interposed. If the latter, surgical intervention may be at least considered. If the former, the condition is perhaps still not irremediable, but the approach will be through other than surgical channels. The present report is concerned with demonstrating that in cats avulsion of ventral spinal roots is compatible with regenerative activity on the part of the neurons involved, even to the extent of functional reinnervation of denervated muscle. With full realization that species and age influence greatly the vigor of regenerative processes in the peripheral nervous system, and that the cat ranks high in respect to that function and man low, the observations are nevertheless offered as an invitation to reexamine the regenerative capacity of nervous tissue similarly damaged in man.

EVIDENCE

Procedure.—Four young adult cats were used. In 3 of these animals the right ventral roots from the sixth cervical to the second thoracic segment were separated from the dorsal roots extradurally and cut distally, at their junction with the dorsal root ganglia. The dural investment of each ventral root was then clipped and slit around the stump until the fan of rootlets was exposed. These were clamped lengthwise in a fine, curved clamp and pulled from the cord, centrally, with a steady even pull to bring out as long a stump as possible. By this procedure the dural investment of the cord was left intact except that immediately surrounding each emerging ventral root. In the fourth animal only three roots, the seventh cervical to the first thoracic, were so treated, but, in addition, the dorsal roots and ganglia were excised, not avulsed, which emptied the intervertebral

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foramens of nerve tissue. This last animal was killed after four weeks, and the other 3 after four, six and twelve months, respectively. All the animals were fixed by intra-aortic injection of a 20 per cent concentration of neutral solution of formaldehyde U. S. P., after preliminary flushing of the vascular system with saline solution. Observations were made on the living animals, on the spinal cords at autopsy and on microscopic preparations of affected parts of the cords and skeletal musculature.

Observations on the Living Animals.—During life the cats exhibited an extent of motor paralysis consistent with their lesions: with five roots cut, complete paralysis of the musculature of the related extremity, and with three roots cut, somewhat less. The paralyzed muscles wasted and contracture resulted. There was also a partial Horner syndrome in the eye on the side of the operation. The animals surviving six months or less made no appreciable recovery of the lost motor functions, even the partial Horner syndrome persisting. During the second half-year, however, the animal surviving longest gradually reestablished some unquestionable control of the skeletal musculature, useful at the shoulder and elbow and demonstrable as fascicular twitches, and even coarser contractions, in the flexors and extensors of the forearm in response to passive stretch. The toes were still tightly fixed in contracture. The partial Horner syndrome was still in evidence, although minimal. Functionally, the large motor fibers had made appreciable recovery, and possibly the smaller preganglionic sympathetic fibers as well.

Autopsy Observations.—The five segments of the cord selected for histologic preparation were not closely examined; that is, the meninges and scar were not disturbed. The remaining segments, thirteen in all, were carefully freed of loose tissue, including the dura, to expose the area for emergence of ventral rootlets. The dorsal rootlets were clipped to improve the view from that direction. In every segment so examined ventral rootlets were clearly to be seen, emerging from the cord. The longer the duration since operation, the better were they developed, but at four months, the earliest of these gross examinations, they were clearly defined and were whitish, as though myelinated. The most cephalad rootlets of a segment were often distinctly thicker and more myelinated in appearance than the middle and caudal segments, an observation suggesting that these longer and obliquely coursing rootlets had been less severely damaged at avulsion. Even at operation it had been evident that some rootlets were breaking off short or just flush with the surface of the cord while others were pulling out fairly deeply. All the grossly visible rootlets turned laterally and plunged into the dense scar tissue, closing the apertures in the dura, where they could be followed no farther. In 1 animal, which survived four months, just dorsal to each of the five reconstituting ventral roots the cord had herniated laterally to form a round nodule 1 to 2 mm. in diameter,

with lateral distortion of both the white and the gray matter, closely confined to that portion only, of each segment. Curiously, in no other animal did anything corresponding to this develop; yet there is nothing in the operative records to explain this singular occurrence.

Microscopic Study of Spinal Roots and Cord.—Specimens consisting of an entire segment of the cord together with the attached roots and ganglion of each side and scar on the one side were prepared according to Cuajunco's [1] modification of Bielschowsky's silver technic and sectioned in series transversely at 15 microns. Figure 1 shows one of these sections. From the cat killed after four weeks all three segments, from the seventh cervical to the first thoracic, were taken, but from the cats surviving four and six months the eighth cervical segment only was used. No histologic preparations were made from the cord of the animal surviving a year, the prior examination of the

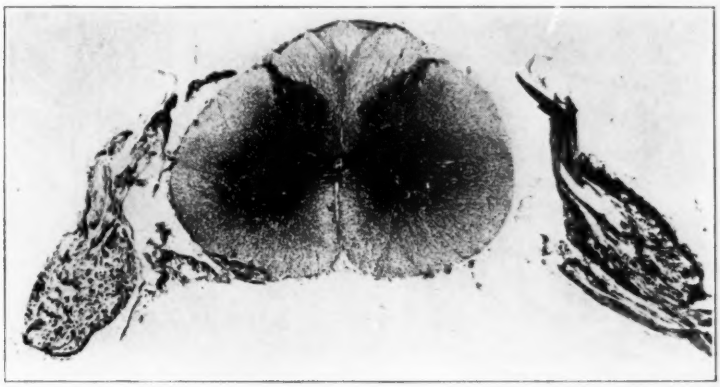

Fig. 1.—Section of spinal cord and roots from the caudal end of the eighth cervical segment four months after avulsion of the right ventral roots (the left side in the photograph). Note the shrunken anterior horn and the reduced thickness of the anterolateral white column, the tracts of emergent rootlets on both sides and the mat of regenerating fibers formed over the emerging rootlets on the affected side. Bielschowsky silver stain.

other specimens and the gross examination having made fairly certain what one could expect to find.

Microscopic examination of the sections of the cord showed even at first glance the tremendous vigor of the regenerative process in every animal. Emerging from the spaces normally emitting the ventral rootlets were nerve fibers, few and fine in the cat surviving one month; more numerous, and both fine and unmyelinated and larger and myelinated, with longer survival. Figure 2 *B*, *D* and *E* show such rootlets

1. Cuajunco, F.: Embryology of the Neuromuscular Spindle, Contrib. Embryol. **19**:45, 1927.

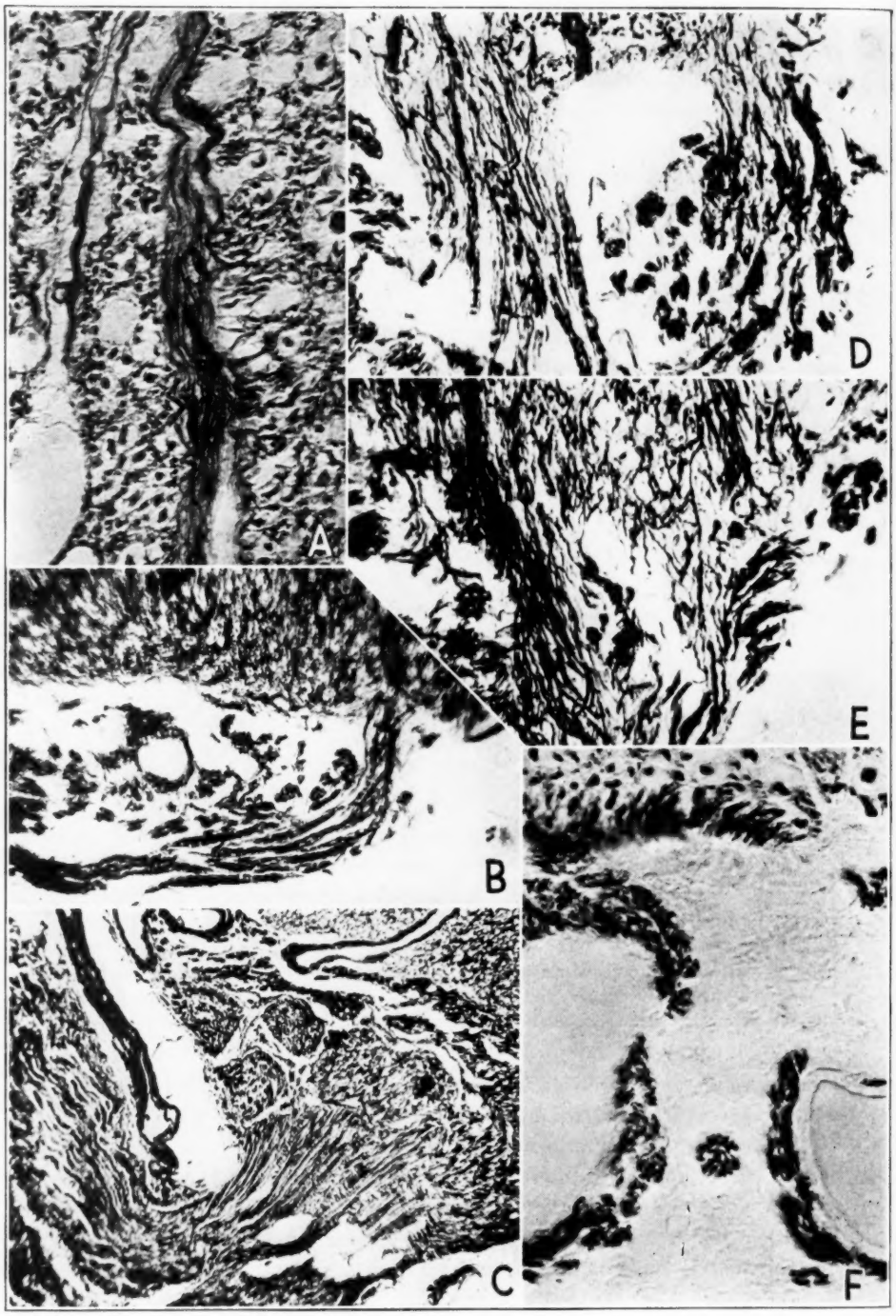

Figure 2

(See legend on opposite page)

after six months' survival. By far the greater number of these fibers turned decidedly laterally, as seen in *B*, and reconstituted the rootlets which were grossly visible at autopsy. Figure 2 *C* shows one of the larger collections of regenerating fibers forming out of a mat of fibers at the surface of the cord and sweeping laterally toward the intervertebral foramen.

More striking, however, than these regenerating rootlets were the single fibers and small groups which escaped from the main bundles into the arachnoid tissue. There they multipled in a riotous fashion into a prodigious number of unmyelinated and intensely argyrophilic fibers, which filled the loose connective tissue of the meninges, formed dense layers in the adventitia around blood vessels and ran in clusters and larger bundles in all directions. Figure 2 *B*, *D* and *E* show such fibers leaving the emerging rootlets, and figure 2 *F*, the dense investment of a good-sized artery and vein and smaller bundles in the arachnoid. The directions of growth of these vagrant fibers were interesting. The meninges dorsolateral and ventromedial to the line of emerging root fibers seemed equally open to them, with the adventitia of blood vessels especially inviting. At one month they had penetrated the ventromedian sulcus to its depth. Fiber bundles were present dorsal to the dorsal roots, however, only in the cat in which the dorsal roots were also removed. The region of intact ventral roots on the other side of the cord was, as it were, hostile territory; the regenerating fibers approached, but did not enter regardless of how long the elapsed time since operation: four weeks or six months. Some small fiber bundles penetrated the cord again in the adventitia of blood vessels, and where this took place far laterally, their being emergent fibers was

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EXPLANATION OF FIGURE 2

Unretouched photomicrographs of Bielschowsky silver preparations.

A, tract of regenerating ventral rootlet deep in the white matter of the seventh cervical segment four weeks after avulsion of the ventral roots. Magnification × 333. *B*, emerging ventral rootlet six months after avulsion. The fibers inside the cord are unmyelinated and intensely argyrophilic, but just outside they begin to myelinate. Magnification × 55. *C*, large-sized rootlet forming from a dense mat of regenerating fibers at the surface of the cord and sweeping laterally toward the intervertebral foramen, six months after avulsion of the ventral roots. Magnification × 25. *D*, two small ventral rootlets emerging from an uninjured part of the cord surface and remyelinating as they turn laterally. Magnification × 120. *E*, two similar small rootlets emerging from a region of injury to the surface of the cord, with fibers sweeping out from the white matter of the anterior column between them. Magnification × 120. *F*, regenerating nerve fibers filling the adventitia of a medium-sized vein (left) and artery (right) and forming bundles in the arachnoid four weeks after avulsion of the ventral roots. Magnification × 333.

out of the question. But this was a rare occurrence. No fibers grew in or on the dura where it was free of scar tissue. The scar filling the intervertebral foramen showed the usual florid picture of fibers growing in a moderately dense connective tissue, with many examples of spiral formation and fountain spraying. And the reconstituted rootlets, many of which were fairly well ordered as long as they lay in loose arachnoid tissue, plunged into this scar and were confounded. Here and there, as shown in figures 1 and *2 C*, regenerating fibers had formed dense, tangled mats applied to the surface of the cord in the region of the emerging rootlets, especially where the pial membrane was damaged. These tended to disorder the reformation of the rootlets, although the large rootlet shown in figure *2 C* arose in just such a plaque.

Within the spinal cord, the tracts for emergence of ventral root fibers were clear in all the specimens—obviously, the preexisting tracts. Figure 1 shows them at a low magnification, and figure *2 A*, at a higher. Some had few or perhaps no fiber occupants; most had a number. There was plain evidence of sclerosis in some of the tracts, the fibrous tissue being laid down lengthwise, and little evidence of it in others. Adjacent tracts might be sclerosed, the one heavily and the other little, if at all, and nerve fibers seemed to emerge equally freely regardless of these conditions.

The fibers emerging along the tracts varied greatly in appearance, which depended partly on the time of survival and partly, apparently, on the accident of how deeply individual fibers were torn out. The four week specimens contained more fibers that compared favorably with the control side for size and myelination than did the longer-surviving specimens. These appeared to be fibers which had broken off short and still retained their original myelination. In the specimens taken later, perhaps because the avulsion was more thorough, or perhaps because the sclerosis resulted in subsequent demyelination, there were few such fibers. In all the specimens, however, by far the greater number of fibers in the tracts, even deep in and adjacent to the gray matter, were fine, intensely argyrophilic, seemingly unmyelinated and often irregular in their course—typical regenerating fibers. Figure *2 A* shows some of these from deep within the white matter at four weeks.

Throughout all these variously disposed masses and bundles of regenerating fibers, both inside and outside the cord, multiplication was going on. The divisions, usually by multiple longitudinal splitting, could be seen deep within the rootlet tracts in the cord, as in figure *2 A*, and more often just inside the cord. But the numbers of fibers leaving the cord were still relatively few, and the rootlet bundles were loosely formed, as shown in figures *2 B* and *D*. Immediately outside the cord, how-

ever, division accelerated rapidly, producing, as the bundles passed distally, the densely packed reconstituted rootlets and giving rise to the sprouts to the arachnoid tissue. Figure *2 B* and *D* show the quantity of this multiplication in rootlets as little involved in injury or scarring of the cord as could be found; figure *2 C* and *E*, the quantity apparently stimulated by graver injury to the cord.

If one may judge the amount of opposition to the regenerating fibers as in proportion to their multiplication, especially to the fantastic forms which this takes, the tracts within the cord must be fairly open and easily traversed. Resistance is met first at the passage from the tracts into the pia-arachnoid, and increasingly from that point distally, out to the dural scar. Certainly, end knobs, such as generally indicate blockage of growth in either the central or the peripheral nervous system, were not seen at all in the tracts; the multiplication of fibers there was not excessive, and spirals and other complicated figures of impeded regeneration were seen at the exit only, and rarely even there. In contrast, all these were increasingly in evidence from the point of emergence of the rootlets laterally to the intervertebral foramen. In a previous publication by Westbrook and me [2] dealing with the dorsal roots of the four week specimens, we could not resist publishing the best picture obtained of one of these spirals at the point of emergence.

In the specimens taken at one month the regenerating fibers did not appear to be remyelinated, though without a specific myelin stain this does not mean that no remyelination had taken place. In the specimens taken at four and six months, although myelinated fibers were almost wanting deep within the rootlet tract in the cord, numbers of fibers just inside and leaving the cord were heavily myelinated, presenting a fairly normal appearance. Especially was this true of fibers turning laterally from the point of emergence in the reconstituted rootlets. Characteristically, the fibers began to be myelinated a little distance from their emergence from the cord, as is apparent in figure *2 B* and *D*, the bulk of the fibers showing at their emergence, as in their course within the cord, the intense silver staining of unmyelinated regenerating axons. Even in the best reconstituted rootlets, however, the myelinated fibers were still greatly outnumbered by the unmyelinated fibers clustering between them. And spirals and other fantastic formations of unmyelinated axons frequently invested the myelinated fibers. Only rarely were the fibers exploring the meninges or filling the adventitia of blood vessels myelinated.

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2. Westbrook, W. H. L., Jr., and Tower, S. S.: An Analysis of the Problem of Emergent Fibers in Posterior Spinal Roots, Dealing with the Rate of Growth of Extraneous Fibers into the Roots After Ganglionectomy, J. Comp. Neurol. **72:** 383, 1940.

Although regenerating ventral rootlets were the most conspicuous source of fibers for the florid growth seen in the specimens they were not the only one. The white matter of the anterior column also contributed, and in no small way, though only where the surface of the cord had been injured. The surface layer of arachnoid-pia-neuroglia appeared to be impenetrable to nerve fibers from either side so long as it was intact. The regenerating fibers clambered in hordes over its outer surface but entered the cord only in the adventitia of blood vessels, while from inside fibers emerged only in what were clearly preexisting rootlet tracts. But where this characteristically staining surface layer was injured, as had happened in a number of places, the fibers of the white matter poured out to join the proliferating swarm. Figure 2 *E* shows this in its most frequent occurrence, between two closely adjacent rootlets, themselves also regenerating, where the surface layer had apparently been torn away in the avulsion. What might be the end result of this growth, should fibers of such origin ultimately terminate in motor end plates on skeletal muscle, cannot be hazarded.

Deeper than the surface, the white matter of the cord was gravely damaged only in the specimens taken at four weeks. These showed much fiber loss of traumatic origin in both the ventral and the lateral column, as well as the emptying of the posterior column due to section of the dorsal roots. Avulsion of the other ventral roots was apparently more smoothly executed, and with the longer passage of time the debris was cleared up and the spaces closed in. But comparison in figure 1 of the thickness of the white matter in the region of emerging ventral rootlets on the two sides gives a measure of the fibers lost.

The anterior horn on the side of operation was noticeably smaller in area than that on the control side in every specimen. Figure 1 shows the difference at four months. On looking more closely, one saw that a great number of cells had disappeared altogether from all specimens, though in the specimens taken at four weeks some debris could usually be made out. But more significant than this destruction is the fact that many of the cells had survived the trauma of having their axons torn out. A rough estimate of the percentage of cells surviving was attempted, as an index to the number of ventral root fibers potentially available for regrowth. The four week specimens had suffered far the gravest loss of cells, the seventh cervical segment on the side of operation possessing never more than half the cell complement of the control side. In ten sections selected at random 1 to 19 large motor type cells were counted on the affected side, as compared with 36 to 46 cells for the control side. Possibly the additional trauma of the dorsal root section, with the attendant reduction in blood supply to the cord, may have contributed to this loss. In the longer-

surviving specimens the cell loss was exceedingly variable throughout the segments, and in the different cell groups in one section, the amount depending probably on the hazard of how deeply the rootlets were torn out. But nowhere did cell counts on the two sides show a loss greater than 50 per cent. Generally speaking, the more cephalic portions of the segments, where the roots were apparently less deeply avulsed, had suffered less. And the larger, more laterally situated cells were generally present in greater number than the smaller, more medially situated cells, possibly because the longer, curved track of the root fibers from the lateral cells cushioned, as it were, the shock of avulsion to a degree that the shorter, more direct course of the fibers from the ventromedial cells could not.

Although no Nissl stains were made, the cells surviving at four weeks looked sick, with eccentric nuclei and seemingly shrunken dendrites. By four months, however, and six months also, the surviving cells were healthy in appearance, and not noticeably smaller than corresponding cells on the control side, with their nuclei centrally located, neurofibrillae clearly stained and no visible pathologic features.

Microscopic Examination of Skeletal Muscle.—The entire fifth interosseous muscle from both forepaws and part of the fourth interosseous muscle were prepared according to the Bielschowsky silver method, the entire first muscle being cut longitudinally at 15 microns, the second, transversely at 10 microns.

Thorough examination of the specimens taken four months after root avulsion showed no motor end plates or motor nerve fibers, only sensory innervation. After six months, however, scattered patches of reinnervated muscle fibers could be found, although this reinnervation had not been detected functionally. Figure 3 shows one of the regenerating nerve fibers branching to form plaques on two muscle fibers. The reinnervated muscle fibers are thicker and more deeply staining than the noninnervated and atrophic fibers in the same field. And the accumulation of nuclei to form the sole plate is conspicuous even where the reinnervating fiber is of very immature appearance, in striking contrast to the lack of identifiable sole plates on atrophic fibers six months after denervation. Apparently, the reassembly of the appropriate nuclei takes place rapidly under the stimulus of reinnervation.

Within the nerve trunks the fibers were still sparse, and with the four month preparation as a standard, it seemed that most of them must be sensory or sympathetic. But among the muscle fibers, copious and somewhat erratic branching greatly increased their number. Up to the final branchings the regenerating fibers occupied neurilemma sheaths which appeared to have the disposition of the old nerve branches. Some of the more florid terminal branching seemed to be

free of this pattern. As they approached the muscle fibers, the reinnervating nerve fibers were unmyelinated and unusually argyrophilic. Within the nerve trunks the presence of the sensory and sympathetic fibers of all sizes made it impossible to distinguish the regenerating fibers with certainty, but groups of intensely argyrophilic fibers were suspect.

The specimens taken a year after root avulsion showed somewhat more extensive reinnervation than that just described, but still very immature. None of these interosseous muscles had recovered function

Fig. 3.—Regenerating nerve fiber branching and forming motor end plates on two muscle fibers. Magnification × 615.

sufficient to enable the cat to spread the toes when reaching for support. And the toes were still firmly flexed and adducted in contracture.

CONCLUSION

The assumption that ventral nerve roots cannot regenerate if avulsed from the spinal cord is clearly unfounded as a general proposition. Avulsion of the ventral roots in cats, causing some fibers to break off outside the cord, others flush with the cord and still others deep within the cord, damages many of the related anterior horn cells

irremediably so that they degenerate and disappear. But many cells also survive and regenerate their axons. The regenerating axons can be seen growing and multiplying in the rootlet tracts deep within the cord with singularly little evidence of obstruction until they emerge into the mesodermal connective tissues. And even there some factor operates to converge the reforming rootlets toward the intervertebral foramens; perhaps an attraction emanating from the scar tissue in the dural apertures or from the distal cut end of the ventral root, or, more likely, a directional organization of the scar tissue in the arachnoid along the lines of the avulsion.

While still within the cord, the regenerating ventral root fibers are strikingly not subject to the conditions which block regrowth of nerve fibers generally within the central nervous system. Moreover, the ventral root exit does not present the impenetrable barrier to growing nerve fibers that the dorsal root entry does (Tower [3]). More detailed knowledge of the arrangement of the supporting tissues in these two junctional zones might throw light on such significant differences, especially, perhaps, in relation to the development of the neuroglia-neurilemma sheaths of the two roots. Recent experimental study of the sheathing of root fibers in chick embryos (Jones [4]) has indicated that the neural crest gives rise to the sheath cells of the dorsal root, and the neural tube, to the sheath cells of the ventral root which migrate out along the fibers. With neuroglia and neurilemma developing thus in continuity from within the cord to the periphery on the ventral root fibers, it is understandable that the rootlet tract should offer no special obstacle to regeneration of these fibers. In the dorsal root, on the contrary, where the two tissues meet secondarily, making a sharply defined junction, this junction, also understandably, clearly offers the first impediment to the reentry of growing nerve fibers (Tower [3]).

That the cat can repair avulsed ventral spinal nerve roots is, of course, no guarantee that man can do likewise. However, since the general frustration of axonal regeneration in the central nervous system does not apply to fibers growing in the ventral rootlet tracts, and since the large impediment to regeneration of ventral spinal nerve roots is the impediment offered to regeneration anywhere in the peripheral nervous system, namely, mesodermal connective tissue, especially in scar formation, an open mind toward the possibility of regeneration of ventral roots in man, perhaps with surgical intervention to cope

3. Tower, S. S.: A Search for Trophic Influence of Posterior Spinal Roots on Skeletal Muscle, with a Note on the Nerve Fibers Found in the Proximal Stumps of the Roots After Excision of the Root Ganglia, Brain **54**:99, 1931.

4. Jones, D. S.: Studies on the Origin of Sheath Cells and Sympathetic Ganglia in the Chick, Anat. Rec. **73**:343, 1939.

with scar tissue in the spinal canal, and with care for the musculature for the period of years that may be required for regrowth, might alter the now hopeless prognosis for this condition. With interest in the regenerative capacities of all parts of the nervous system, currently stimulated, on the one hand, by the intensified study of poliomyelitis and, on the other, by the war, these observations are offered to invite reexamination of the regenerative capacity of avulsed ventral spinal roots in man.

SUMMARY

Ventral spinal nerve roots were avulsed from the cord in 4 cats and the animals killed after periods of from four weeks to one year. Evidence of regeneration was sought during life and found in the longest-surviving animal. Reinnervation of the denervated skeletal muscle was demonstrated histologically in the 2 longest-surviving animals. Evidence of vigorous regeneration on the part of the ventral root fibers was observed either grossly at autopsy or on microscopic examination in all the animals, beginning deep in the rootlet tracts of the cord. The cells of the cord were variously affected, many being destroyed completely, others surviving. The assumption that ventral nerve roots cannot regenerate if avulsed from the cord is, therefore, obviously unfounded as a generality. The evidence invites reconsideration of the potential regenerative capacity of the ventral spinal roots after similar damage in man.

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STUDIES IN DISEASES OF MUSCLE

XI. PROGRESSIVE MUSCULAR ATROPHY: REPORT OF A CASE WITH UNUSUAL FEATURES; EFFECT OF PROSTIGMINE AND PHYSOSTIGMINE ON FASCICULATIONS; METABOLISM OF ASCORBIC ACID

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The present paper may properly be considered as consisting of three parts: (1) report on a patient in whom the clinical picture was that of progressive chronic anterior poliomyelitis with onset of symptoms in earliest childhood and a course that had been slowly progressive for about twenty-six years; (2) investigations on the effect of prostigmine and physostigmine on muscular fasciculations in this patient and in other subjects with progressive muscular atrophy, with comparison of the effects on the adventitious movements and those on choline esterase activity, and (3) a study of the metabolism of ascorbic acid in this and in other patients after administration of large amounts of the vitamin for prolonged periods.

METHODS

During the period of investigation the patient was in the research metabolism ward of the New York Hospital, where the diet could be rigorously supervised. A creatinine-creatine-free diet constant in its content of calories, protein and ascorbic acid from day to day was given. All specimens of urine were collected in dark-colored bottles containing acetic acid and immediately placed in the refrigerator to preserve the vitamin. The specimens of each period of exactly twenty-four hours were mixed together and analyzed for amounts of preformed creatinine, creatine, total nitrogen and ascorbic acid by the methods discussed in earlier reports.[1]

The name "fasciculations" is used in this report for the adventitious movements commonly seen in the muscles of patients with progressive disease of the anterior horn cells. These contractions usually are referred to as "fibrillations" in the clinical

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

From the Departments of Medicine and Psychiatry, Cornell University Medical College; the Russell Sage Institute of Pathology, and the New York Hospital.

1. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38**:992-1024 (Nov.) 1937. Milhorat, A. T.; Bartels, W. E., and Toscani, V.: Effect of Hepatic Injury on Vitamin C Excretion in Fasting Dogs, Proc. Soc. Exper. Biol. & Med. **45**:394-397, 1940.

literature, a designation that probably should be limited to the spontaneous fibrillar twitching that has its onset on the fourth or fifth day after denervation (Langley and Kato [2]) and can best be demonstrated by viewing the exposed surface of the muscle. When fibrillations are well developed, the muscle shows a continuously quivering surface. Usually these fibrillations cannot be demonstrated in patients by clinical examination. On the other hand, the spontaneous muscular contractions discussed in this report are visible through the skin and subcutaneous tissues. Denny-Brown and Pennybacker [3] pointed out that the muscular elements involved are larger than a single muscle fiber and probably represent the fibers in a motor unit. Clark [4] counted an average of about 120 muscle fibers in the motor unit of the soleus muscle of the cat. Denny-Brown and Pennybacker suggested the name "fasciculations," and it appears advisable to use the term to distinguish this type of contraction from the "fibrillations" discussed by Langley and Kato.

In a series of investigations the effect of prostigmine and physostigmine on the muscular fasciculations was observed. The procedure was as follows: During the morning, while the patient was lying comfortably in bed, careful note was made by simple inspection of the sites and amount of fasciculation. The patient was then given a subcutaneous injection of either prostigmine methylsulfate or physostigmine sulfate. Changes in fasciculations and any side effects, such as sweating, pallor, abdominal cramps, nausea and vomiting and changes in pulse rate, were recorded at various times. The choline esterase activity of the serum was determined before the administration of the drug and at different intervals after the injection, including the time when the effect of the drug was considered to be at its maximum. For the estimation of the choline esterase activity of the serum, the procedure previously discussed [5] was used.

REPORT OF CASE

History.—An unmarried woman aged 28 was admitted to the New York Hospital on Sept. 23, 1940. Her birth and development during the first year of life were said to have been normal. She did not walk until the age of 2 years. The gait from the beginning was waddling, and there was lordosis. She was overweight until about the age of 8, when she lost weight steadily, and has since been very thin and underweight. During her earliest days in school it was noted that she was unable to hold a pencil in her hand in normal fashion. The hands were weak, and she appeared unable to use the thumb in writing. At about the same time the patient complained of weakness of the lower extremities, but despite this she was able to walk considerable distances to and from school. The disability progressed very slowly, but at the age of about 13 the weakness increased more rapidly. During the next three years the disability in the lower extremities had progressed to the point where she was unable to walk more than five blocks on level ground. The difficulty in using the hands likewise increased, and at the age of 16 the patient was unable to extend the fingers. At about the same time she noted numerous fasciculations of the muscles of the trunk and four extremities.

2. Langley, J. N., and Kato, T.: The Physiological Action of Physostigmine and Its Action on Denervated Skeletal Muscle, J. Physiol. **49**:410, 1915.

3. Denny-Brown, D. E., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311, 1938.

4. Clark, D. A.: Muscle Counts of Motor Units: A Study in Innervation Ratios, Am. J. Physiol. **96**:296-304, 1931.

5. Milhorat, A. T.: The Choline-Esterase Activity of the Blood Serum in Disease, J. Clin. Investigation **17**:649-657, 1938.

Muscular weakness and wasting progressed slowly but steadily from the age of 16 until about two years prior to the date of her admission to the hospital. During this two year period progression of weakness, especially of the lower extremities, was more rapid. At the time of her admission the patient complained of being able to walk only short distances, and then with difficulty, and of tiring easily when standing. She stated that she usually felt somewhat weaker during the

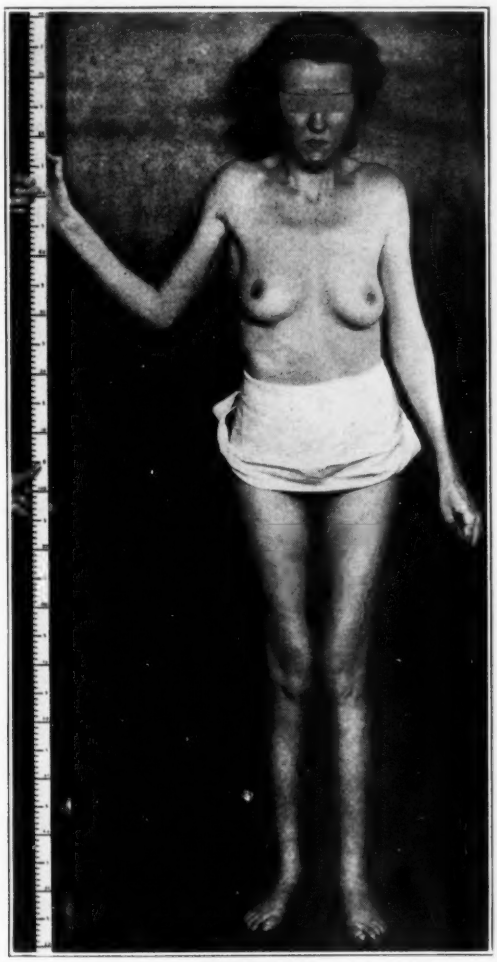

Fig. 1.—Photograph of patient with progressive muscular atrophy.

early hours of the day than in the afternoon. The rest of the history with reference to the nervous and muscular systems was negative. There was no record of a preceding febrile condition.

The familial history revealed no instance of similar illness or of any disease of the muscles or nervous system.

Examination.—The patient was thin and poorly nourished, with small wasted muscles, moderate dorsal scoliosis and considerable lordosis (fig. 1). Her gait

was slow and waddling. She had considerable difficulty in raising the trunk to a sitting position when in bed and was unable to assume the upright position without support. Practically all the muscles of the extremities and trunk showed reduction in volume and power. Muscular wasting was more evident in the peripheral portions of the extremities. The hands showed advanced wasting of the thenar and hypothenar eminences and of the interosseous muscles. The first interphalangeal joints of the fingers were ankylosed in the position of flexion. The hands presented a moderately advanced main en griffe appearance (fig. 2). The feet were flat and showed considerable wasting of the muscles. The patient was unable to move the feet against even slight passive resistance. All the tendon reflexes were absent. The plantar response was of flexor type bilaterally. Over the entire trunk and the four extremities numerous fasciculations were present. These were increased when the muscles were tapped with a percussion hammer. Sensibility for pain, light touch, vibration, position and temperature was intact. The peripheral nerve trunks were not enlarged or tender on palpation. The weight was 43 Kg.

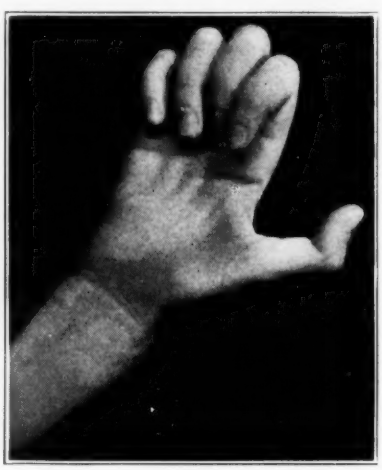

Fig. 2.—Hand of patient with progressive muscular atrophy, whose photograph is shown in figure 1.

Laboratory Data.—The concentrations of urea nitrogen, nonprotein nitrogen, calcium and phosphorus in the blood were normal. Determinations of the prothrombin level of the blood, the urea clearance test for renal function and gastric analysis showed no abnormality. The activity of the choline esterase of the serum was 3 units (normal value); the phosphatase level was normal. The basal metabolic rates on four occasions were between +3 and +6 per cent. Two electrocardiograms were normal. Roentgenologic examination showed accentuation of the lumbosacral curvature of the spine and slight diffuse decalcification of the bones of the hands, spine and pelvis. The average daily urinary output of preformed creatinine and creatine was 0.700 and 0.200 Gm., respectively. The creatinine index (milligrams of preformed creatinine per kilogram of body weight) was 16. The creatine tolerance (retention of ingested creatine) was 33.5 per cent. Microscopic examination of a piece of a tissue removed from the left deltoid muscle showed

the fibers to be normal, except those in one small area, where they were in an early stage of necrosis. There was slight increase in the connective tissue.

Subsequent Course.—One and a half years later the patient reported that the muscular disability had progressed only slightly since she had left the hospital.

The clinical picture is typical of progressive muscular atrophy resulting from disease of the anterior horn cells. However, the onset during the first five years of life and the long course are most unusual, since progressive muscular atrophy of this type almost always begins between the ages of 25 and 55 and usually terminates fatally in from two to five years. In cases of progressive muscular atrophy of the Charcot-Marie-Tooth peroneal type, an early age of onset is not unusual, and a course of many years' duration is common; however, the absence of even minor defects in sensibility, the extent and activity of fasciculations and the apparently simultaneous involvement of all four extremities at so early an age as that of this patient are features making this diagnosis less likely. Any of these phenomena can occur in certain cases of progressive peroneal muscular atrophy, but their concomitant appearance in a patient with considerable lordosis is unusual for this disease. The negative familial history apparently is of little significance in making the diagnosis. Whereas many patients with progressive peroneal muscular atrophy give a history of some other person in the family with the disease, perhaps an equal number give a negative familial history.

A diagnosis of peripheral neuritis is not justified in this case because of the absence of all subjective and objective involvement of sensibility. Progressive muscular dystrophy, in rare instances, can begin in peripheral groups of muscles, but the number and character of the fasciculations in this case make such a diagnosis unlikely. Moreover, microscopic examination of the piece of muscle removed for biopsy revealed changes more commonly seen in muscles wasted as a result of disease of the anterior horns than in muscles with progressive dystrophy. In cases of the former condition Slauck [6] observed small groups of muscle fibers in different stages of atrophy surrounded by entirely normal fibers, whereas in cases of progressive muscular dystrophy the atrophic and normal fibers were seen lying side by side without the arrangement observed in disease of the anterior horn cells.

From the point of view of diagnosis of any of the muscular syndromes, this case presents many extraordinary features. We never have seen another case with these characteristics and have been unable to find a report of a similar case in an extensive survey of the literature.

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6. Slauck, A.: Beiträge zur Kenntnis der Muskelpathologie, Ztschr. f. d. ges. Neurol. u. Psychiat. **71**:352-356, 1921.

EFFECT OF PROSTIGMINE AND PHYSOSTIGMINE ON FASCICULATIONS

The accompanying table gives a summary of the data observed on this patient. It will be noted that both prostigmine and physostigmine increased muscular fasciculations, but that prostigmine had considerably more effect on skeletal muscles and less effect on other organs than had physostigmine. These differences occurred even when the drugs were given in amounts that decreased the choline esterase activity of the serum to similar levels. Significant increase in muscular fasciculations accompanied only slight changes in esterase activity after prostigmine had been given, whereas similar changes in esterase activity induced by physostigmine were without effect on the fasciculations. Similar investigations made on 4 other patients with muscular atrophy subsequent to disease of the spinal cord gave the same results. Moreover, prostigmine produced fasciculations in muscles in which no adventitious movements previously had been observed. For example, numerous fasciculations were

Effect of Prostigmine Methylsulfate and Physostigmine Sulfate on Muscular Fasciculations

Serum Esterase Activity, Units		Muscular Effects *	Side Effects †	Drug, Mg.
Resting Level	Level After Drug			
3.02	2.60	+++	—	Prostigmine methyl sulfate, 0.5
2.91	1.95	++++	—	Prostigmine methyl sulfate, 1.0
3.01	2.27	—	—	Physostigmine sulfate, 0.6
2.93	1.98	+	+++	Physostigmine sulfate 1.2

* Increase in fasciculations.

† Dizziness, sweating, nausea and abdominal cramps.

regularly produced in the face and tongue by prostigmine, although these were never seen when the patient had not been given the drug.

Physostigmine often induced side effects even in doses that had little effect on fasciculations. The administration of prostigmine was followed by side effects only when large doses were given and considerable increase in fasciculations was produced. The side effects of either drug were abolished readily by atropine. On the other hand, the effect on fasciculations appeared to be uninfluenced by atropine. Furthermore, atropine was without effect on the spontaneous adventitious movements. Langley and Kato,[2] in their studies on denervated muscle, expressed the belief that physostigmine had both a central and a peripheral action and that atropine opposed the former but did not affect the latter. Russel, Odom and McEachern [7] found atropine to be without influence either on the fasciculations produced by prostigmine in animals or on the effect of prostigmine on fasciculations occurring in patients with

7. Russel, C. K.; Odom, G., and McEachern, D.: Physiological and Chemical Studies of Neuromuscular Disorders, Tr. Am. Neurol. A. **64**:120-124, 1938.

progressive muscular atrophy. Denny-Brown and Pennybacker [8] expressed the opinion that fasciculations in progressive muscular atrophy may be the result of intermittent discharges from the diseased motor neurons. However, the peripheral origin of fasciculations in this disease is suggested by their persistence after spinal anesthesia [8] or blocking of the peripheral nerve by procaine.[9] It appears that the two views can be reconciled by the formulation that the slowly degenerating muscle fibers are abnormally sensitive to stimulation and that the involuntary impulses increase the fasciculations. Increased sensitivity of the muscles in progressive muscular atrophy is shown by the observation recorded here, namely, that amounts of prostigmine that are without effect in normal subjects can induce fasciculations in muscles in which no adventitious movements had previously been seen. These effects of prostigmine and physostigmine on fasciculations cannot be explained entirely by the inhibitory effect on the choline esterase activity. The situation is analogous to that seen in cases of myasthenia gravis, in which prostigmine has greater muscular effects than has physostigmine even when the changes in choline esterase activity induced by the two drugs are similar.[10] It is likely that the effects of the drugs on fasciculations in progressive muscular atrophy and on muscular function in myasthenia gravis are due partly to their antiesterase action and partly to direct action on the muscle.

METABOLISM OF ASCORBIC ACID

The urinary output of ascorbic acid was determined daily for two months. During a period in which the patient was given a creatinine-creatine–free diet containing about 50 mg. of the vitamin the average daily excretion was 26 mg. The addition of 500 mg. of crystalline ascorbic acid to the diet increased the output to around 115 mg. On days when 500 mg. of the vitamin was given subcutaneously in place of a dietary supplement of similar amounts the output was unchanged. An increase in the dietary supplements of ascorbic acid to 700 mg. (500 mg. of crystalline ascorbic acid and 200 mg. in tomato juice) induced only a slight rise in the daily output, namely to a level of 130 mg. The amounts of the vitamin in the urine represented only 16 per cent of the

8. Grund, G.: Ueber Bewegungsvorgänge des menschlichen quergestreiften Muskels, die von der motorischen Vorderhornganglienzelle unabhängig sind. Beitrag zur Pathologie rheumatischer Krankheitszustände, Deutsche med. Wchnschr. **64**: 488, 1938; Ueber die Entstehung der fibrillären Muskelzuckungen bei spinalen Amyotrophien, Deutsche Ztschr. f. Nervenh. **145**:99-109, 1937.

9. de Jong, H., and Simons, D. J.: A Comparative Study of Fibrillation and Tremor, J. A. M. A. **118**:702-705 (Feb. 28) 1942. Russel, Odom and McEachern.[7]

10. Milhorat, A. T.: Studies in Diseases of Muscle: X. Prostigmine and Physostigmine in the Treatment of Myasthenia Gravis, Arch. Neurol. & Psychiat. **46**:800-834 (Nov.) 1941.

amount ingested. On days when a total of 825 mg. of ascorbic acid was given (200 mg. subcutaneously, 500 mg. orally and 125 mg. in tomato juice) an average of 150 mg. was excreted (17 per cent). During the period when the 500 mg. of the vitamin was given daily the amount of ascorbic acid in the plasma was 0.5 mg. per hundred cubic centimeters (normal values are from 0.7 to 1.4 mg.); when 700 mg. was given the amount in the plasma was 0.9 mg. per hundred cubic centimeters.

The urinary excretion of ascorbic acid was studied in 7 other patients to whom large doses of the vitamin were given. Three patients with progressive muscular dystrophy, 1 patient with Friedreich's disease and 1 subject with limited muscular wasting subsequent to an acute attack of anterior poliomyelitis fifteen years previously, who were given from 400 to 500 mg. of ascorbic acid daily for periods of several weeks, excreted from 60 to 90 per cent of the vitamin. When similar amounts of the vitamin were given to another patient with extensive muscular wasting due to chronic progressive anterior poliomyelitis and 1 patient with dermatomyositis and severe Raynaud's syndrome, only about 20 per cent of the administered dose was excreted.

The data make it improbable that the low urinary output can be ascribed to abnormal absorption from the intestine, impaired function of the kidneys or previous deficiency of the vitamin. The excretion was unchanged by parenteral administration of the vitamin; tests of renal function were normal, and the output did not increase even after a period of two months, during which at least 500 mg. of ascorbic acid was given daily. It is of interest that the other patient with progressive muscular atrophy subsequent to disease of the anterior horn cells likewise excreted small amounts of the vitamin while receiving a large amount. The third patient showing a low urinary output had extensive muscular involvement with severe Raynaud's disease. The factors determining the low urinary output of ascorbic acid of these 3 patients are not known. The excretion of the vitamin by the other 5 patients in this series was similar to that observed by Storvick and Hauck [11] for normal subjects receiving large amounts of ascorbic acid.

The low excretion of ascorbic acid by the 3 patients was unexpected, since the original objective of the study was the effect of the vitamin on creatinuria. Hirata and Suzuki [12] reported diminution in the output of creatine in cases of progressive muscular dystrophy when amounts of from 200 to 500 mg. of ascorbic acid were administered daily for periods of about two weeks. However, in all 8 patients in the present

11. Storvick, C. A., and Hauck, H. M.: Effect of Controlled Ascorbic Acid Ingestion upon Urinary Excretion and Plasma Concentration of Ascorbic Acid in Normal Adults, J. Nutrition **23**:111-123, 1942.

12. Hirata, Y., and Suzuki, K.: A New Information Concerning Progressive Muscular Atrophy and Vitamin-C, Orient. J. Dis. Infants **18**:83, 1935; Dystrophia Musculorum Progressiva und Vitamin C, Klin. Wchnschr. **16**:1019, 1937.

series ascorbic acid was without effect on the daily excretion of creatine and creatinine. It is difficult to explain the results of Hirata and Suzuki, but it appears that other factors still unrecognized may have played a significant role in their investigations. Thus, Milhorat, Weber and Toscani [13] observed a definite decrease in the excretion of creatine in 2 patients with dermatomyositis when large amounts of wheat germ and ascorbic acid were given, whereas ascorbic acid alone was without effect. Similar results were observed by Milhorat and Toscani [14] in a patient with progressive muscular dystrophy. Whether the patients of Hirata and Suzuki suffered from previous deficiency of ascorbic acid or whether substances similar to those present in wheat germ unknowingly were given together with the vitamin cannot be stated at this time. While ascorbic acid appears to be without value in the treatment of the muscular diseases,[15] there is evidence that the metabolism of the vitamin is related significantly to that of creatine (Milhorat, Hardy, Bartels and Toscani [16]).

SUMMARY

The case history of an adult with progressive muscular atrophy is presented. The features were typical of chronic anterior poliomyelitis, with the unusual feature of onset of disability in infancy.

Prostigmine and physostigmine increased the fasciculations in this patient and in other subjects with progressive muscular atrophy. Prostigmine had greater effects on fasciculations than had physostigmine even when the inhibitory effect on choline esterase activity of the serum was the same. It is postulated that the effect on fasciculations is due only partly to the antiesterase activity of the drugs and that these drugs have a direct action on skeletal muscle. In addition to increasing fasciculations in areas where they already are active, prostigmine and physostigmine may induce fasciculations in areas previously free of them, even when the drugs are given in doses that are without effect in normal subjects.

Two patients with progressive muscular atrophy who received large amounts of ascorbic acid excreted in the urine an abnormally low percentage of the administered vitamin.

525 East Sixty-Eighth Street.

13. Milhorat, A. T.; Weber, F. C., and Toscani, V.: Metabolic Studies in Dermatomyositis, with a Note on the Effect of Wheat Germ, Proc. Soc. Exper. Biol. & Med. **43**:470-473, 1940.

14. Milhorat, A. T., and Toscani, V.: Unpublished data.

15. Milhorat, A. T.: Treatment of Diseases of Muscle, New York State J. Med., to be published.

16. Milhorat, A. T.; Hardy, J. D.; Bartels, W. E., and Toscani, V.: Effect of Shivering, Iodoacetate, and Epinephrine on Vitamin C and Creatine Excretion in Fasting Dogs, Proc. Soc. Exper. Biol. & Med. **45**:397-399, 1940.

FASCICULAR MUSCLE TWITCHINGS IN AMYOTROPHIC LATERAL SCLEROSIS

THEIR ORIGIN

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Grund [1] and later Shelden and Woltman [2] found that the intrathecal injection of procaine in an amount sufficient to produce complete motor paralysis of the legs did not abolish the muscular fibrillations in patients with amyotrophic lateral sclerosis. These experiments were interpreted as showing that the impulses causing these fibrillations did not arise from the cell bodies of the motor neurons of the ventral horn. Each of these investigations consisted of but 1 experiment; the nature of the muscular twitchings was not controlled by electrical recordings, and no further attempt was made to locate the source of the impulses causing the fibrillations. For these reasons the present study was undertaken.

PROCEDURE

Three patients with typical and advanced amyotrophic lateral sclerosis and 2 others with progressive muscular atrophy with muscular fibrillation [3] were utilized in this study. Three of the patients exhibited many and 2 relatively infrequent muscular fibrillations at the time they were studied.

The muscular fibrillations were observed clinically, and their action potentials were picked up by microelectrodes, amplified by a Grass condenser-coupled amplifier and recorded by ink writers.

To produce paralysis of individual or groups of muscles, a 1 or 2 per cent solution of procaine hydrochloride was injected directly into the nerve supply, or

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*A Commonwealth Fund Fellow. Dr. Swank is now serving as captain in the Medical Corps of the United States Army.

From the Department of Medicine, Harvard Medical School, and the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

1. Grund, G.: Ueber die Entstehung der fibrillären Muskelzuckungen bei spinalen Amyotrophien, Deutsche Ztschr. f. Nervenh. **145**:99, 1938.

2. Shelden, C. H., and Woltman, H. W.: Origin of Fibrillary Twitchings, Proc. Staff Meet., Mayo Clin. **15**:646, 1940.

3. Swank, R. L., and Putnam, T. J.: Amyotrophic Lateral Sclerosis and Related Conditions: Clinical Analysis, to be published.

200 mg. of procaine hydrochloride crystals dissolved in 2 cc. of spinal fluid was injected intrathecally. In 2 instances the degree of paralysis was checked by stimulating the nerve above the point of procainization with a faradic current furnished by a Harvard inductorium. Currents as strong as the patient could tolerate did not produce a response in the muscle at a time when paralysis of voluntary effort was complete.

RESULTS

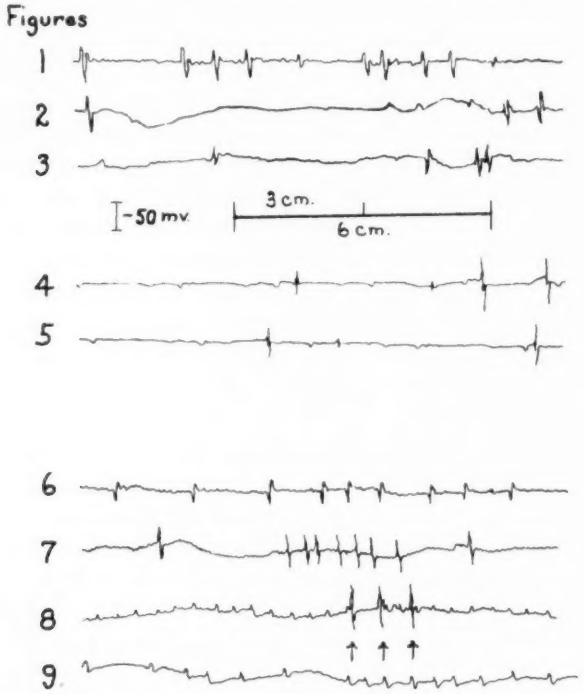
A. Spinal Anesthesia.—Spinal anesthesia was produced in 2 patients. In 1 of these patients fibrillations, which were numerous in most of the muscles of the lower extremities before anesthesia appeared to be greatly reduced in number. In the figure, *1* is a control record from the medial portion of the rectus femoris muscle just above the knee; *2* was taken from the same muscle and *3*, from the peroneus longus muscle after spinal anesthesia had produced complete paralysis of the lower extremities. These records indicate that the spinal anesthesia had reduced fibrillations 50 to 65 per cent quantitatively, the nature of their action potentials remaining essentially unchanged. In a second patient complete motor paralysis was produced in the same way, with similar results.

B. Peroneal (Anterior Tibial) Nerve.—In 5 experiments (3 patients) procaine was injected at the point where the nerve passes lateral to the fibula. The injection was followed by complete paralysis of the dorsal flexor muscles of the foot in each patient. In 1 of these patients (2 experiments) the fibrillations, which were numerous, were completely abolished by this procedure. In the other 2 patients (3 experiments) the fibrillations, which were infrequent during the control period, were but slightly decreased in number. In 1 of the latter 2 patients fibrillations were abolished subsequently by injecting procaine directly into the muscle in a line about 4 cm. above the recording electrode. In the other patient it was necessary to inject procaine into the muscle 2 cm. above the recording electrode to produce a pronounced reduction in fibrillations, and only after the procaine had been injected directly into the fibrillating muscle were the twitchings abolished. Tracing 4 is a control record from the anterior tibial muscle in the first of the latter 2 patients. Tracing 5 was recorded from the same muscle after foot drop was produced by injection into the peroneal nerve at the fibula. Immediately after this procaine was injected into the muscle about 4 cm. above the electrode, after which no action potentials were recorded.

C. Ulnar Nerve.—Procaine was injected into the ulnar nerve at the elbow, with the production of complete paralysis of the hypothenar muscles in 3 experiments (1 patient). This procedure reduced the number of visible fibrillations, but did not abolish them entirely. In each of these experiments subsequent injection into the ulnar nerve at the wrist abolished all visible fibrillations. Tracing 6 is a record of the action potentials produced by fibrillary twitchings in the hypothenar muscles during the control period. Tracing 7 shows a burst of similar potentials after injection into the ulnar nerve at the elbow. Occasionally

much smaller action potentials, not accompanied by visible muscular fibrillations, were observed after this injection. These are shown in *8*, three much larger potentials accompanied by visible fibrillations being indicated by arrows. After injection into the ulnar nerve at the wrist occasional bursts of the very small action potentials not accompanied by visible fibrillations were still seen (tracing *9*), both spontaneously and after manipulation of the little finger.

D. General Observations.—Stretching and then relaxing a muscle frequently produced bursts of fibrillations. Also any body movement, for



In this figure, *1, 2* and *3* are records of action potentials produced by fibrillating muscle bundles in the lower extremities before (*1*) and after (*2* and *3*) spinal anesthesia. The paper speed was 6 cm. per second.

Tracings *4* and *5* are records of action potentials produced by fibrillating muscle bundles in the anterior tibial muscle before (*4*) and after (*5*) the injection of procaine hydrochloride into the peroneal nerve lateral to the fibula. The paper speed was 3 cm. per second.

Tracings *6, 7, 8* and *9* are records of action potentials produced by fibrillating muscle bundles in the hypothenar muscles before (*6*) and after (*7* and *8*) injection of procaine hydrochloride into the ulnar nerve at the elbow and at the wrist (*9*). The paper speed was 6 cm. per second.

example, hyperventilation or waving the arms, increased or brought out fibrillations in muscles being studied even though they remained at rest.

For these reasons great care was necessary to insure that the conditions under which the action potentials were studied varied as little as possible. Prostigmine methylsulfate injected subcutaneously appeared to increase the number of fibrillations. After procainization of the nerve supply to the muscle prostigmine did not cause the fibrillations to reappear.

COMMENT

In the discussion which follows it is assumed that the injection of procaine into a peripheral nerve, as performed in these experiments, blocks completely the passage of stimuli in the motor nerve fiber.

Apparently, in patients with amyotrophic lateral sclerosis, the stimuli which cause the muscular fasciculations can have their origin in a peripheral nerve fiber independent of its cell body. Probably the cell body can also originate these stimuli, since in 2 patients the fibrillations, which were many, were reduced approximately 50 per cent by spinal anesthesia. However, the stimuli causing them may have arisen from the peripheral nerve process adjacent to the cell body, rather than from the cell body itself. In 2 other patients with relatively few fibrillations nearly all of these stimuli appeared to arise from the distal part of the peripheral nerve process, since blocking the nerve with procaine a few centimeters above its termination only slightly altered the fibrillations (figure, *4* and *5*).

In another study [3] it was suggested that the presence of many fibrillations in a patient with amyotrophic lateral sclerosis indicated rapidly progressive, and few fibrillations slowly progressive, amyotrophy. According to our studies, in cases of the rapidly progressive type a large part of the neuron, especially its distal portion, appears to be affected, whereas in cases of the latter, or slowly progressive, type the disturbance appears to be limited to or especially marked near the termination of the nerve fiber. This indicates that the functional impairment in the lower motor neuron in these cases develops near its termination first and progresses centralward. Perhaps the ultimate degeneration is of the same type as that seen with thiamine deficiency.[4] Pathologic [5] and clinical [3] studies suggest that the degeneration in the pyramidal tracts is also retrograde in patients with amyotrophic lateral sclerosis.

The nature of the change in the peripheral nerves which provokes these uncontrollable stimuli is not clear. There seems to be an element of increased irritability, which is supported by the presence of a definitely

4. Swank, R. L.: Avian Thiamin Deficiency: A Correlation of the Pathology and Clinical Behavior, J. Exper. Med. **71**:683, 1940. Swank, R. L., and Prados, M.: Avian Thiamine Deficiency: II. Pathologic Changes in the Brain and Cranial Nerves (Especially the Vestibular) and Their Relation to the Clinical Behavior, Arch. Neurol. & Psychiat. **47**:97 (Jan.) 1942.

5. Davison, C.: Amyotrophic Lateral Sclerosis: Origin and Extent of the Upper Motor Neuron Lesion, Arch. Neurol. & Psychiat. **46**:1039 (Dec.) 1941.

lowered chronaxia early in the disease.[6] Many of the observations of Denny-Brown and Pennybacker[7] suggest the same origin. Perhaps "spilling over" of some substance which normally gives rise to these stimuli or products of abnormal metabolism in the neuron are capable of provoking them.

Although the number of action potentials was reduced, their amplitude was not notably changed by spinal anesthesia. However, in 2 experiments in which the ulnar nerve was blocked at the elbow and wrist, and in 1 instance in which the peroneal nerve was blocked at the fibula, many low amplitude potentials, not accompanied by visible fibrillations, appeared in the record (figure, *8* and *9*). It is possible that these low amplitude potentials were produced by contracting muscle groups at some distance from the electrode, although this seems unlikely, as they were not present before anesthesia. An alternative explanation is suggested by the fact that a single motor nerve fiber must bifurcate many times before its termination in order to innervate as many as one hundred and sixty-five muscle fibers,[8] the motor neuron unit. It is known that many of these bifurcations occur in the peripheral nerve.[9] Stimuli arising independently in a subdivision of the main nerve fiber could cause a part of the motor neuron unit to contract and produce the smaller action potentials. The nerve block central to this point would prevent a motor unit response from a stimulus originating proximally or spread of the stimulus to the entire unit. The weakness of the contraction would prevent it from being visible through the skin.

CONCLUSIONS

The stimuli provoking fascicular twitchings which appear in the muscles of patients with amyotrophic lateral sclerosis appear to be derived mainly from peripheral motor nerve fibers. In patients with numerous fibrillations these stimuli seem to arise from the entire nerve process and probably also to a less extent from the cell body. In other patients, with few fibrillations, the stimuli appear to arise almost entirely from near or at the termination of the nerve fibers.

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6. Bourguignon, G.: La chronaxie dans la sclérose latérale amyotrophique, Rev. neurol. **32**:808, 1925.

7. Denny-Brown, D., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311, 1938.

8. Clark, D. A.: Muscle Counts of Motor Units: A Study in Innervation Ratios, Am. J. Physiol. **96**:296, 1931.

9. Eccles, J. S., and Sherrington, C. S.: Number and Contraction-Values of Individual Motor-Units Examined in Some Muscles of the Limb, Proc. Roy. Soc., London, s.B **106**:326, 1930.

FAMILIAL TYPE OF PARALYSIS IN INFANTS AND ITS RELATIONSHIP TO OTHER HEREDOFAMILIAL DISORDERS

A CLINICOPATHOLOGIC STUDY

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In spite of the clear differentiation between various heredofamilial neurologic syndromes, many instances of transitional forms have been described from both the clinical and the pathologic viewpoint, particularly among the syndromes of Friedreich's ataxia, Marie's heredocerebellar ataxia, Charcot-Marie-Tooth peroneal muscular atrophy, hereditary spastic paralysis and Leber's hereditary optic nerve atrophy. This report concerns a disease occurring in 3 siblings which does not easily fall under any previously described disease entity. Clinically the condition in 1 case resembled infantile progressive spinal atrophy (Werdnig-Hoffmann disease). Histopathologically it was related to amaurotic family idiocy (Tay-Sachs disease) but presented changes that are also seen in other, supposedly unrelated, forms of heredofamilial disorder.

REPORT OF CASES

The 3 cases occurred in a family in which no previous nervous disorder was known. Both parents were born in Ireland, of Irish stock. During the course of twenty years the mother had been pregnant fourteen times, eleven of the pregnancies terminating in full term deliveries and three in miscarriages. Three of the eleven children, the fourth, seventh and eleventh (fig. 1), were afflicted with the disease. All of the others are living and well except the second, who died at the age of 6 weeks of "inflammation of the bowel." The report of the first case was obtained from the University of California Hospital; the second, from the Children's Hospital of Oakland, Calif., and the third case was studied in the department of pediatrics of the Stanford University School of Medicine.

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CASE 1.—The child, a boy, was delivered normally. After a gastrointestinal upset at the age of 6 months, he was said not to be "as active as other children of his age." Otherwise, as far as can be ascertained, his development was normal until he was 17 months old, when his neck was noted to be weak. After an attack of bronchitis, at the age of 19 months, he rapidly became weaker and was unable to hold up his head or bear his weight on his legs. He lost the ability to use the few words that he previously had learned and had difficulty in swallowing. He seemed able to recognize his parents. Physical examination at the age of 20 months revealed that the child was fairly well developed; nothing abnormal was noted except in the neurologic examination. Convergent strabismus of both eyes was present; the optic disks were somewhat pale, perhaps indicating incipient optic nerve atrophy. The pupils reacted to light. The radial, knee and ankle jerks were all elicitable. No pathologic reflexes were noted. The superficial reflexes were not obtained. The child was rated an imbecile in an intelligence test. He died at the age of 24 months, probably of bronchopneumonia.

CASE 2.—This child, a girl, was born three years after the first patient. She was seen at regular intervals in an outpatient clinic and by visiting nurses and was regarded as normal during the first year of life. Her only illnesses were

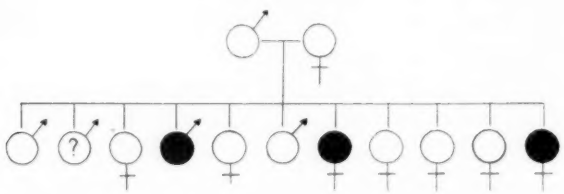

Fig. 1.—Familial distribution of cases. Offspring are shown in the order of birth. The black circles indicate affected offspring; the hollow circles, healthy children.

attacks of measles and pertussis. At the age of 13 months a visiting nurse remarked that the child seemed in good condition except that she could not yet stand and "seemed too heavy for her feet." A month later the clinic physician made the following note: "The baby appears well nourished. Examination reveals essentially nothing of significance except for retarded physical development. She is probably normal mentally." At the age of 15 months she was able to sit up for an hour at a time but still was unable to stand by herself. At 20 months there appeared attacks of cyanosis, labored respiration and "spasms." Her intelligence was regarded as below that of the other members of the family at this age. Physical examination at 21 months of age showed the child to be well nourished and able to sit up for short periods. Strabismus was present; the pupils reacted well to light. The musculature seemed soft and flabby. The patellar, biceps and superficial abdominal reflexes were not obtained. The Wassermann reaction of the blood was negative. The only remarkable laboratory observation was a leukocyte count of 32,600 (polymorphonuclear leukocytes, 84 per cent; lymphocytes, 16 per cent). During the next four months the child became unable to move either her arms or her legs, and the "spasms" continued. She died of bronchopneumonia at the age of 24 months.

CASE 3.—This child, a girl, was born ten years after the patient in the preceding case. The mother felt the child was "not right" from the age of 7 months; the clinic physicians, however, could detect nothing remarkable at this time. At the age of 13 months it was believed that her physical development was retarded. The psychologist's report on a mental rating stated: "The child is slightly retarded. She is 14 months old and does the things expected of a child 1 year old and probably some more, but the examiner was strange and so could not get the most from her." At the age of 16 months, although able to crawl, she could not walk. During the following four months the child's condition became progressively worse. She lost the ability to crawl and remained in a supine position almost constantly. She did, however, reach for objects and play with things in her hands. She was able to flex her legs on her abdomen but seemed perfectly limp when placed on her feet. She was also observed to have a number of attacks, each lasting a few seconds, in which she became quiet, her pupils dilated and her face was "fixed, with a dull, staring look in her eyes." There was no motor seizure. She began to have difficulty in swallowing at the age of 19 months and became unable to speak. Three days before her death she often seemed fairly observant, while at other times she appeared to be unaware of her surroundings. She cried only with great effort and then produced but little noise. Physical examination at this time revealed the following condition: Right internal strabismus was present; the pupils reacted to light and in accommodation. The liver and spleen were not palpable. There was pronounced lumbar kyphosis. The extremities seemed completely relaxed, and the musculature was weak and flabby. She was able to hold objects in her hands, raise her arms up to her abdomen and move her toes slightly. There was flaccid paralysis of all other movements of the extremities. The knee jerks, although present, were difficult to elicit. The superficial abdominal reflexes were absent. Some fibrillations were noted in the muscles of the feet. Examination of the blood and urine revealed nothing of importance. She died at the age of 23 months; shortly before death she experienced difficulty in breathing, and her temperature rose to 42 C. (107.6 F.).

In all 3 cases the onset was first noted at about the first birthday, and death resulted near the second. A flaccid type of paralysis, involving especially the trunk and the proximal portions of the extremities, was present; the lower extremities appeared to be more seriously involved than the upper. The tendon reflexes were active in the first case, absent in the second and sluggish in the third. The musculature was flabby in all 3 cases, but no definite atrophy was detected. Fibrillations in the feet were noted in the third case. Mental impairment probably existed, though in varying degrees, in all the cases. This was an outspoken manifestation, however, only in case 1 (in which the child was rated as an imbecile). Seizures were observed in the second and third cases. Blindness was not apparent in any of the cases, although a possible beginning optic nerve atrophy was observed in the first. In case 3 the child was able to grasp for objects shortly before death. Strabismus was noted in each case.

The clinical diagnosis in these cases was difficult. The signs and symptoms, however, approached those of infantile amaurotic family

idiocy (Tay-Sachs disease), as well as those of infantile progressive muscular atrophy (Werdnig-Hoffmann disease), both familial disorders with an invariably fatal outcome. In no case was the cherry red spot characteristic of the former disease observed in the macula. In other respects the first case resembled Tay-Sachs disease: progressive paralysis with retention of tendon reflexes, mental deterioration and questionable beginning optic nerve atrophy. In the second and third cases no pronounced degree of mental impairment and no abnormal visual signs, except strabismus, were noted. Seizures, observed in both these cases, have been reported in association with Tay-Sachs disease. In spite of this, however, these cases were thought to be instances of infantile progressive muscular atrophy, inasmuch as the outstanding difficulty was flaccid paralysis with absent or sluggish tendon jerks. While atrophy was impossible to detect because of the abundant layer of subcutaneous fat, fibrillations and diminished reaction to faradic current were observed in 1 of the cases.

Postmortem Examination in Case 3.—Gross Description: The musculature of the back and abdomen appeared to be poorly developed, the latter being covered by a 2 cm. layer of subcutaneous fat. Under a similar thick layer of fat in the region of the calves, the muscles were severely atrophied. Aside from congestion in both lungs, nothing remarkable was noted in the viscera. Macroscopic examination of the nervous system revealed nothing abnormal except for the small size of the cerebellum.

Microscopic Examination of the Nervous System: The following staining methods were employed: hematoxylin and eosin, phosphotungstic acid hematoxylin, cresyl violet, nile blue, scarlet red, Schaffer's modification of the Pal-Weigert technic and the methods of Bielschowsky, Mallory, Cajal and Kanzler.

Spinal Cord: The cellular changes (fig. 2) were similar at all levels of the cord. These changes were noted in all the cell columns but were especially noticeable in the nucleus dorsalis (Clarke's column) and in the cells of the posterior horn. Many of the cells were swollen. Some of the cell bodies had become rounded or pear shaped, while others retained a nearly normal form. Some appeared to be round and homogeneous, staining deeply with a variety of methods. The Nissl substance had disappeared completely in some cells and partially in others; in still other cells, especially those of the anterior horn, it seemed to be normal. In sections stained by the Bielschowsky method, the neurofibrils, while appearing to be distributed normally in some cells, were often pushed to the periphery and replaced by a granular cytoplasm, or a network of thick fibrils was seen inside the cell body. With the myelin stain many of the cells were observed to contain hematoxylinophilic granules (prelipoids). No neutral fat was present in the ganglion cells. The nuclei tended to be least affected. Some were located in the central portion of the cell body; however, in many of the seriously involved cells the nucleus was displaced to the periphery or pushed into the base of the swollen dendrite or had completely disappeared. Numerous cells were devoid of processes. In others, however, an irregular swelling of the process was seen, similar to the swelling of the cell. Some of the cells were indistinguishable from the type seen in axonal degeneration. Frequent shadow cells were scattered throughout the nuclear masses. Shrunken pyknotic cells were also observed.

Demyelination of both the lateral and the ventral corticospinal tract occurred throughout their entire course (fig. 3). The posterior column was involved in the thoracic and cervical regions. In the thoracic region an area corresponding to the medial root zone of Flechsig was involved; in the cervical region the fasciculus gracilis and the adjacent portions of the fasciculus cuneatus were affected.

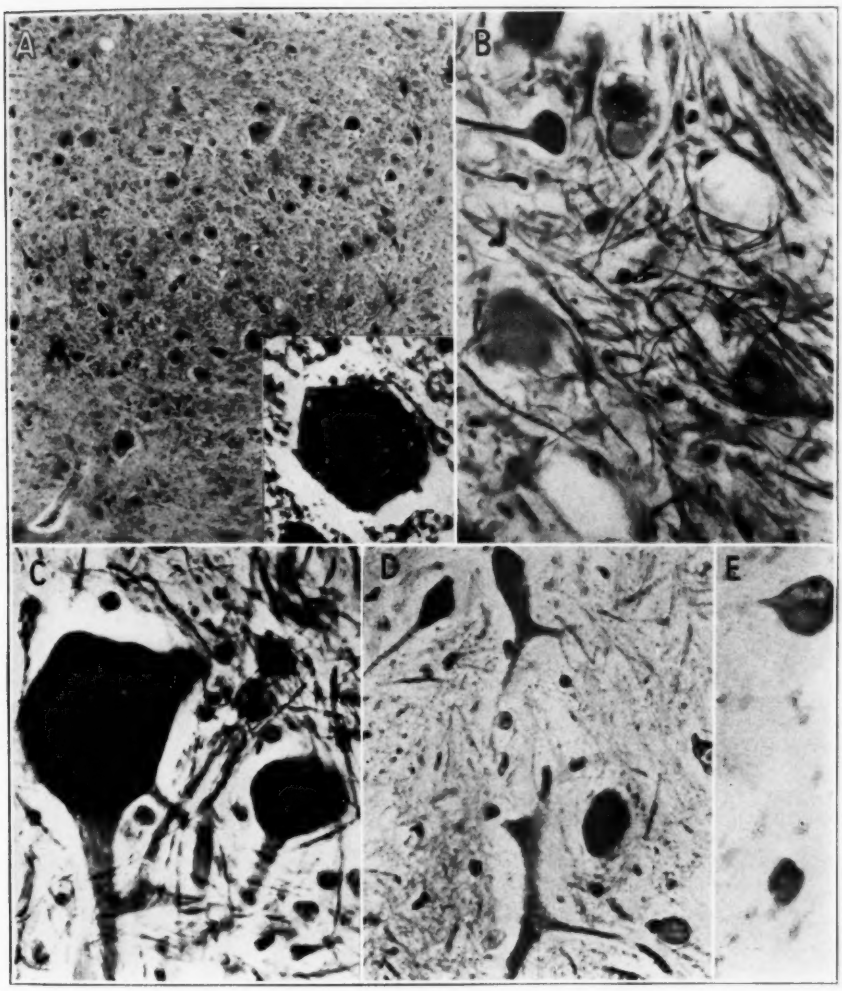

Fig. 2.—Cellular alterations in the spinal cord and medulla. *A*, large, rounded, amorphic cells in the posterior horn; cresyl violet stain. High power view in inset, stained by Bielschowsky method. *B*, mulberry body, shadow cell, empty cell space and shrunken pyknotic cell in the medulla; Bielschowsky stain. *C*, pear-shaped cells in the anterior horn; Bielschowsky stain. *D*, swollen dendrite, pyknotic cells and bloated glia cell in the anterior horn; cresyl violet stain. *E*, cell showing axonal reaction and shadow cell; cresyl violet stain.

The small oval area of Flechsig, composed of descending fibers, was the only afferent pathway involved below the thoracic region.

An increase in number of all types of glia cells was noted throughout the cord and was most evident in the posterior horn and in the area of the lateral

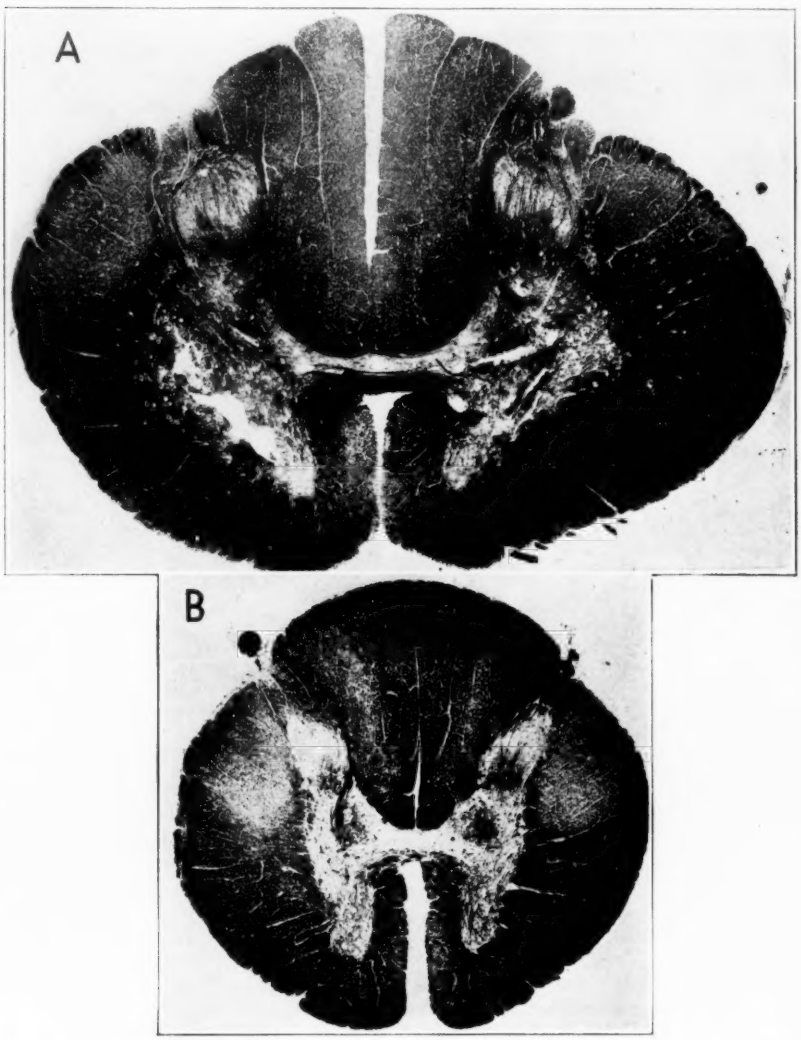

Fig. 3.—Demyelination in the lateral and ventral corticospinal tracts and in the posterior funiculus. In the cervical region (*A*) the demyelination of the posterior funiculus is most evident in the fasciculus gracilis, and in the thoracic region (*B*), in the area corresponding to the middle root zone of Flechsig. Myelin sheath stain.

corticospinal tract (fig. 4). Many swollen astrocytes and fat-laden gitter cells were seen.

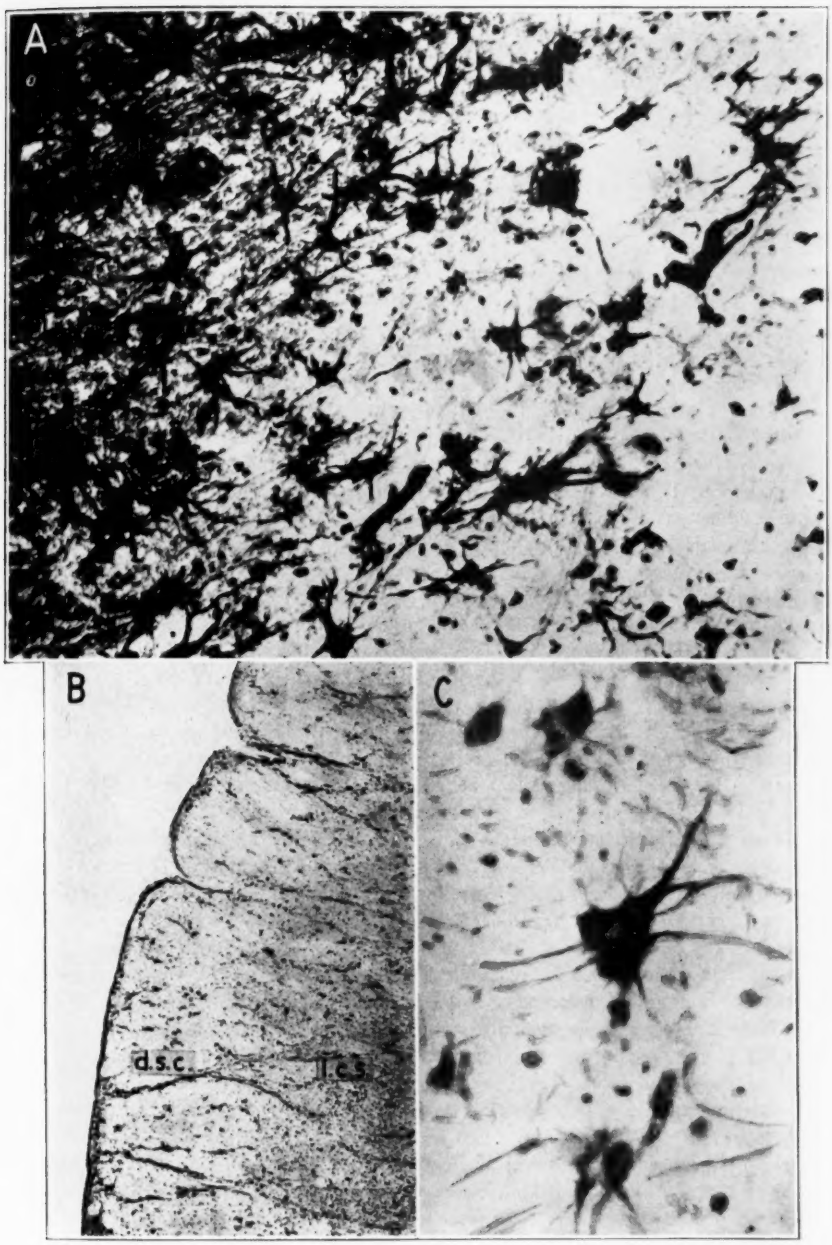

Fig. 4.—Astrocytic gliosis in the spinal cord. *A*, increase in number and size of astrocytes in the posterior horn. *B*, low power view, showing gliosis in the lateral corticospinal tract (*l. c. s.*) and absence of gliosis in the dorsal spinocerebellar tract (*d. s. c.*). *C*, monster astrocytes in the lateral corticospinal tract. Cajal gold chloride–mercury bichloride stain.

Medulla, pons and midbrain: The great majority of the ganglion cells in these structures were involved, the changes resembling those in the spinal cord. Swollen, distorted cells were seen in all nuclear groups, though the cells of the inferior olivary nucleus and the substantia nigra were somewhat less affected than most of the others. So-called mulberry bodies were seen throughout the medulla and pons. Numerous round, homogeneous cells with absence of nuclei, similar to those in the spinal cord, were observed; ghost cells and empty cell spaces were also present (fig. 2 *B*). Satellitosis was seen frequently, although neuronophagia was difficult to find. The restiform body, the brachium pontis and the brachium conjunctivum appeared normal.

Basal ganglia and diencephalon: As a whole these portions of the nervous system were the least disturbed. In the thalamus, globus pallidus and putamen only an occasional cell was involved. The cells of the caudate nucleus, however, seemed to be more disturbed. Practically all of the cells in the periventricular nuclei appeared to be normal. The internal capsule was undergoing degenerative changes; a notable increase in glial elements and the presence of considerable neutral fat in sections stained with scarlet red were noted. No mulberry bodies were observed in this entire region.

Cerebellum: All the folia of the cerebellum (fig. 5) appeared to be reduced in size. Sections from the lingula, culmen, central lobule, folium, uvula and nodule of the vermis and the quadrangular lobe, inferior semilunar lobule and tonsil of the hemisphere were similar in appearance. Disappearance of most of the Purkinje cells was striking. Only a few of these cells remained in each folium, and all of them were damaged. These remaining cells often assumed a bizarre appearance; their Nissl substance had disappeared, the cell body was either swollen or pyknotic, and their dendrites were irregularly enlarged. Neurofibrils were difficult to recognize in the cell body with the Bielschowsky stain, though they were seen in the swollen dendrites. In the absence of the Purkinje cells, the layer of glia cells (Bergmann's glia) between the granular and the molecular layer had increased in size (forming the so-called sheath of Lannois-Paviot). The basket cells and their tangential fibers and pericellular baskets were decreased in number, although those present frequently appeared normal. Pericellular baskets were occasionally seen surrounding empty spaces formerly occupied by Purkinje cells. The granule cells were moderately diminished in number, particularly in the external portion of the layer; the cells, however, appeared normal. The granular layer and the white lamina contained numerous fibrous astrocytes, many being swollen and multinucleated. While the cells of the dentate nucleus seemed to be normal in number, some were involved in the degenerative process.

Cerebral cortex: In general, alterations in cortical structure were not as marked as those in the spinal cord, brain stem and cerebellum. The most severe changes were in the motor area. The general architecture of the cellular laminas was always recognizable. The molecular layer appeared to be more dense than normal. The layer of small pyramidal cells (lamina granularis externa) seemed intact. In the motor area the layer of medium-sized pyramidal cells (III) was poorly developed, and a patchy disappearance of ganglion cells was noted. This was also true of the deeper layers. In the fifth layer no giant pyramidal cells could be detected. The cytoarchitecture of the temporal isocortex was affected to a lesser extent, disappearance of cells in the third layer being infrequent and the deeper layers relatively unimpaired. In the occipital lobe the layer of small pyramidal cells (II) and the layer of large pyramidal cells (IV a) were better developed than the others. Few abnormalities were noted in the cornu ammonis. However, cellular alterations of varying degrees were present in all portions of

the cortex that were examined. The normal contour of the cell was usually retained, even though some swelling was observed; only rarely were balloon-shaped or pear-shaped cells seen. The axis-cylinders were usually intact. Gliosis

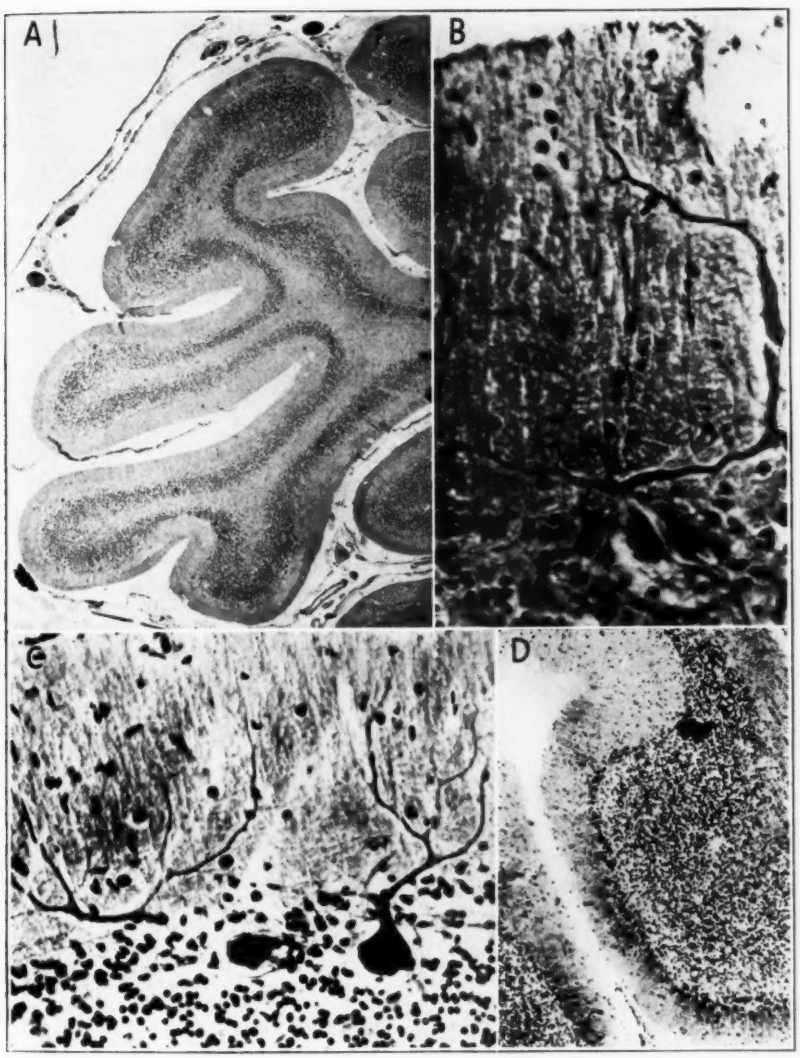

Fig. 5.—Sections of the cerebellum. *A*, low power view, showing small folia and diminution in the number of Purkinje cells (eleven of their cell bodies may be counted); cresyl violet stain. *B* and *C*, abnormal-appearing Purkinje cells, with irregular swelling of antler-like dendrites, and a pericellular basket in *C*; Bielschowsky stain. *D*, proliferation of Bergmann's glia, replacing the Purkinje cells, and rarefaction of granule cells near the molecular layer; phosphotungstic acid hematoxylin stain.

was present throughout the cortex and, to an even greater extent, the subcortical white matter. Regressive changes in the microglia and oligodendroglia were pronounced. Neuronophagia was seen more frequently in the cortex than elsewhere, leaving a residuum of partially destroyed cells and shadow forms.

Meninges: Slight cellular proliferation was noted in the pia-arachnoid, especially over the cerebellum. The cells consisted of fibroblasts, lymphocytes and wandering histiocytes. Some contained lipoidal granules; some were degenerating. A few compound granular cells were also seen.

Blood vessels: Most of the blood vessels were normal in appearance. However, in regions of marked parenchymatous change the blood vessel walls were frequently affected, especially the outer portions. In some the adventitial structures were almost completely destroyed, except for scattered connective tissue fibers and swollen fibroblasts containing lipoidal granules. The muscle cells were sometimes swollen, but the endothelium was usually normal.

Microscopic Appearance of Other Organs: Small bundles of atrophic fibers with some proliferation of the nuclei were seen in sections of voluntary muscle. The heart muscle showed pronounced signs of degeneration; atrophy, swelling and vacuolation were present. The lungs were congested and edematous. Marked swelling and degeneration of cells in the malpighian corpuscles of the spleen were observed. Numerous wandering histiocytes were present in the thymus. With the scarlet red stain neutral fat appeared in some of the Kupffer cells of the liver and the epithelial cells of the convoluted tubules of the kidney. With the Schaffer modification of the Pal-Weigert stain hematoxylinophilic granules (prelipoids) could be seen in many of the visceral organs, including the swollen cells of the malpighian corpuscles of the spleen (fig. 6*A*), the septal cells of the lung, the Kupffer cells of the liver, the muscle fibers of the heart (fig. 6*B*) and all the cellular elements of the thymus. No "foam cells" were observed.

Alterations in structure were noted throughout the entire central nervous system. These changes were greatest in the spinal cord, brain stem and cerebellum. They were least conspicuous in the basal ganglia and diencephalon. The cells and their processes, the glia and the myelin of some ascending and descending pathways were affected.

In the spinal cord, the nuclei of the posterior horn and the nucleus dorsalis were especially disturbed. The cerebellum was reduced in size. Most of the Purkinje cells were missing, and the few that remained were damaged. Bergmann's layer of glia was augmented in size. The granule cells were rarefied, and cell-free patches were noted near the molecular layer. The deeper layers of the cerebral cortex tended to be more involved than the others. The damage was greatest in the motor area, where the layer of giant pyramidal cells appeared to be absent.

The cellular changes consisted, in part, of swelling of the cytoplasm, distortion of the normal cellular architecture, disappearance of the Nissl substance and changes in neurofibrillary structure. Pear-shaped and balloon-shaped cells were observed, but these rarely reached the size ordinarily seen in cases of amaurotic family idiocy. Some of the swollen cells contained hematoxylinophilic granules, indicating the presence of so-called prelipoids. The processes of many of the altered cells were

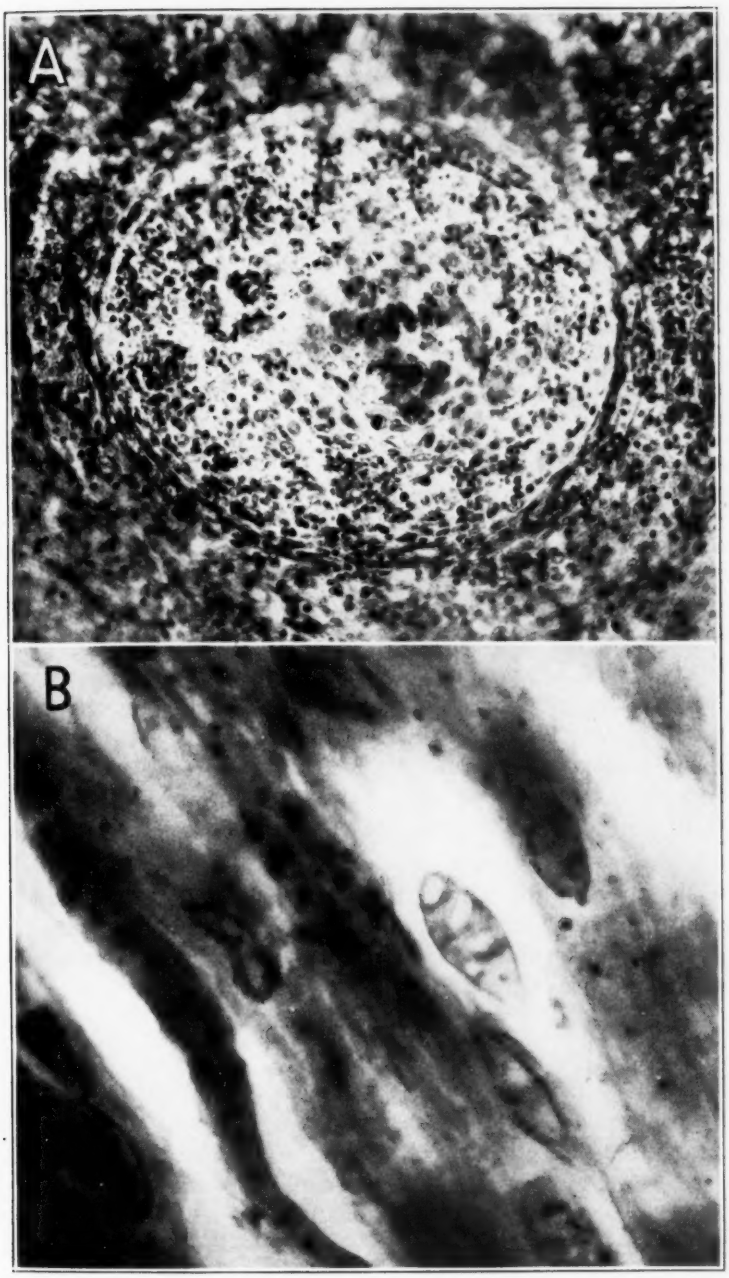

Fig. 6.—*A*, malpighian corpuscle of the spleen, with central necrosis and deposition of hematoxylinophilic granules; Schaffer stain. *B*, heart muscle fibers, showing hematoxylinophilic granules; oil immersion.

decreased or absent; remaining dendrites were sometimes of bizarre shape, with irregular expansions. Changes in the dendrites often resembled those seen in the cells. Shrunken, pyknotic cells, shadow forms and empty cell spaces were observed. The nuclei of these large cells were located at the periphery, or were even pushed into the base of the swollen dendrite.

Increase in glia was observed everywhere in the nervous system. In the basal ganglia this increase seemed to be more pronounced than the cellular alterations. All types of glia cells were involved. Numerous monster astrocytes, often multinucleated, and compound granular corpuscles were present.

Diminution in the number of myelin sheaths was observed in the lateral and ventral corticospinal tracts and in portions of the posterior column, particularly the fasciculus gracilis. The oval area of Flechsig was the only afferent pathway involved below the thoracic region. Glia cells, particularly astrocytes, were increased in these areas. Lack of involvement of the dorsal spinocerebellar tract was remarkable in view of the severe alteration in Clarke's column. In spite of serious impairment of intracerebellar connections, as evidenced by the disappearance of Purkinje cells, all the afferent and efferent cerebellar pathways were relatively intact. The conspicuous gliosis in the myelin-poor portions of the cord (fig. 3 *B*) and the presence of pericellular baskets around cell-free spaces in the cerebellum were evidence that the process was degenerative, rather than due to lack of development of these structures.

Slight cellular proliferation of the pia-arachnoid was observed. Degeneration of the walls of some of the blood vessels, most pronounced in the adventitia, may be interpreted as a secondary reaction to the parenchymatous involvement.

While degeneration of heart muscle, voluntary muscle and the malpighian corpuscles of the spleen was noted, the most striking change in the visceral organs was the appearance of numerous hematoxylinophilic granules in the spleen, liver, lung, heart and thymus.

COMMENT

The familial neurologic disorder that has been described does not readily conform to any previously described disease, either from the clinical or from the pathologic viewpoint. Certain of the changes, however, are shared by a variety of heredofamilial disorders.

Clinically the cases were marked by a flaccid type of paralysis, with retention of tendon jerks in 2 of the cases, absence of abdominal reflexes, loss of speech, difficulty in swallowing, strabismus and varying degrees of impairment of mentation. Seizures were observed in 2 of the 3 cases. Fibrillations and diminished reaction to faradic stimulation were observed

in 1 case and pale optic disks in another. The disease began during the first year of life, and death occurred about the second birthday.

In onset, fatal termination and familial occurrence the disorder was similar to both amaurotic family idiocy (Tay-Sachs disease) and infantile progressive muscular atrophy (Werdnig-Hoffmann disease). The flaccid paralysis and involvement of cranial nerves may be present in either disease. Seizures have been reported only in cases of the former. Against the diagnosis of amaurotic family idiocy are (1) absence of severe mental deterioration in 2 of the cases and (2) lack of visual disturbances. In the third case, in which histologic examination was made, the patient was able to grasp for objects until shortly before death. The absence of amaurosis is evidently exceedingly rare in cases of Tay-Sachs disease. Van Bogaert and others [1] reported the occurrence of idiocy without visual disturbances in a child of a family in which other members had the typical manifestations of the disease; no pathologic verification is available. Sachs [2] stated that in rare instances the visual disturbance may begin late in the course of the disease. In a few other cases reported [3] the cherry red spot has not been observed.

Pathologically, the disease in this case seemed to resemble Tay-Sachs disease more than any other. Swollen, bizarre cells and dendrites were seen which appeared to be identical with the characteristic cells of this disease. Atrophy of the cerebellum and disappearance of the Purkinje cells similar to the alterations in Tay-Sachs disease were present. Involvement of pyramidal tracts, hyperplastic gliosis and "mulberry bodies" were also noted. The increase in glia in the third case was not always related to the cellular alterations—evidence that it was a primary, and not a reactive, phenomenon; this feature has been stressed by some observers in cases of amaurotic family idiocy.[4a] In spite of these similarities, the swelling of the cells was neither as marked nor as striking as is to be expected in characteristic cases of this disorder. In addition, many cells appeared to be undergoing axonal degeneration, and empty cell beds were observed. While involvement of the cortico-spinal tracts has frequently been noted, damage to the posterior column

1. van Bogaert, L.; Sweerts, J., and Bauwens, L.: Sur l'idiotie amaurotique familiale du type Warren-Tay-Sachs. Etude sémiologique du syndrome de décérébration et des automatismes primitifs de l'enfant, Encéphale **27**:196-223, 1932.

2. Sachs, B.: Personal communication to the authors.

3. Epstein, J.: Amaurotic Family Idiocy Without the Classical Cherry-Red Spot, Arch. Pediat. **46**:124-129, 1929. Hassin, G. B., and Parmelee, A. H.: Amaurotic Family Idiocy (Tay-Sachs Type), Am. J. Dis. Child. **35**:87-102 (Jan.) 1928.

4. Wilson, S. A. K.: Neurology, Baltimore, William Wood & Company, 1940, (*a*) p. 884; (*b*) pp. 950 and 954.

is practically unique, except in the case of Frey.[5] This author observed changes in the posterior column beginning in the lower thoracic region, affecting particularly Goll's fasciculus. This is identical with the distribution of the involvement in the present case, except for the changes in the oval area of Flechsig, which have not previously been described.

There was little histologic evidence in the third case to favor the clinical diagnosis of Werdnig-Hoffmann disease, a diagnosis that seemed likely in view of the familial character, rapid course and occurrence of flaccid paralysis with fibrillations. The pathologic changes that have been described usually consist primarily of shrinkage and disappearance of anterior horn cells, and occasionally of the motor nuclei of the medulla, pons and midbrain. Degeneration of the pyramidal tracts has been noted in a high percentage of the cases reported. Zatelli [6] described involvement of Goll's column and of the medium-sized and giant pyramidal cells in the cerebral cortex, changes which were present in this case. It should be noted, moreover, that many of the cases reported as instances of Werdnig-Hoffmann disease have been identified only by their clinical manifestations, without benefit of histologic examination; some may have resembled our case.

In spite of the lack of close similarity to previously described heredofamilial diseases, resemblances not only to the aforementioned entities but to others may be noted. The association of combined degeneration of the pyramidal tracts and the posterior column, particularly of the fasciculus gracilis, has been observed frequently in cases of Friedreich's ataxia and peroneal muscular atrophy (Charcot-Marie-Tooth disease), less frequently in cases of hereditary spastic paralysis [7] and only rarely in cases of amaurotic family idiocy [5] and Werdnig-Hoffmann disease.[6] The additional involvement of the cells of the nucleus dorsalis (Clarke's column) has been reported in association with all these disorders but the last. Similar atrophy of the cerebellum with pronounced reduction in the number of Purkinje cells has been described in cases of Marie's heredocerebellar ataxia, Friedreich's ataxia, hereditary spastic paralysis and amaurotic family idiocy. Reduction or disappearance of pyramidal cells in the motor region, particularly the giant cells and middle-sized

5. Frey, E.: Pathohistologische Untersuchung des Centralnervensystems in einem Falle von Sachs'scher familiärer amaurotische Idiotie, Neurol. Centralbl. **20**:836-843, 1901.

6. Zatelli, T.: Zur Klinik und Pathologie der familiären, frühinfantilen, spinalen, progressiven Muskelatrophie (Typus Werdnig-Hoffmann), Arb. a. d. neurol. Inst. a. d. Wien. Univ. **19**:436-450, 1912.

7. Newmark, L.: Ueber die familiäre spastische Paraplegia, Deutsche Ztschr. f. Nervenh. **27**:1-23, 1904. Kahlstorf, A.: Klinischer und histopathologischer Beitrag zur hereditären spastischen Spinalparalyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:774-780, 1937. Schaffer, K., and Miskolczy, D.: Histopathologie des Neurons, Leipzig, J. A. Barth, 1938, p. 50.

pyramidal cells, has been noted in cases of Friedreich's ataxia,[8] hereditary spastic paralysis,[7] amaurotic family idiocy and Werdnig-Hoffmann disease.[6] Amyotrophy and damage to the anterior horn cells are seen not only in Werdnig-Hoffmann disease and peroneal muscular atrophy but in Friedreich's ataxia.[4b]

It is obvious, therefore, that in this broad group of heredofamilial disorders certain sites in the nervous system are especially vulnerable. This, of course, is not sufficient evidence to warrant the assumption that these disease processes are basically identical. The frequent involvement of the pyramidal tracts and of a portion of the posterior column is of special interest because these pathways are the youngest, both phylogenetically and ontogenetically, in the cord, and hence probably the most susceptible.[9]

The bizarre swelling of cells and dendrites which was present in this case is often considered to be pathognomonic of amaurotic family idiocy. The swollen cells and dendrites noted by Schaffer in a case of family spastic paralysis [7] and the pear-shaped cells seen by Teschler in a case of "chronic progressive amyotrophy" [10] are examples of a similar change, however. The presence of hematoxylinophilic granules, not mentioned in these cases, may be of more diagnostic significance. They were observed not only in the cells of the central nervous system but in many of the visceral organs. Such deposits are generally described as prelipoids (such as phosphatides and cerebrosides). Similar changes in the viscera were noted in cases of amaurotic family idiocy by Kufs [11] (adult type) and by Davison and Jacobson [12] (infantile type), an observation favoring Bielschowsky's concept [13] that this disease is the expression of a general disturbance in lipoid metabolism.

SUMMARY

A disorder occurring in 3 siblings, leading in all of them to a fatal termination at the age of 2 years, is described. The clinical manifesta-

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9. Brouwer, B.: The Significance of Phylogenetic and Ontogenetic Studies for the Neuropathologist, J. Nerv. & Ment. Dis. **51**:113-136, 1920.

10. Teschler, L.: Zur Frage der chronisch progressiven spinalen Amyotrophien (sogenannter Poliomyelitis chronica), Arb. a. d. neurol. Inst. a. d. Wien. Univ. **30**:229-246, 1928.

11. Kufs, H.: Sind die familiär-amaurotische Idiotie (Tay-Sachs) und die Splenohepatomegalie (Niemann-Pick) in ihrer Pathogenese identisch?, Arch. f. Psychiat. **91**:101-106, 1930.

12. Davison, C., and Jacobson, S. A.: Generalized Lipoidosis in a Case of Amaurotic Familial Idiocy, Am. J. Dis. Child. **52**:345-360 (Aug.) 1936.

13. Bielschowsky, M.: Amaurotische Idiotie und lipoidzellige Splenohepatomegalie, J. f. Psychol. u. Neurol. **36**:103-123, 1928.

tions consisted of (1) progressive flaccid paralysis in which the distal portion of the extremities was least involved and the tendon jerks were not necessarily absent; (2) signs of involvement of the brain stem consisting of strabismus, loss of articulation and difficulty in swallowing, and (3) varying degrees of impairment of mentation. Amaurosis was not present. The clinical diagnosis of Werdnig-Hoffmann disease was made in 1 case. In this case diffuse changes were noted post mortem. They were most severe in the spinal cord, brain stem and cerebellum. Swelling and disappearance of cells and dendrites were seen. Pathologic changes in the glia were pronounced. The pyramidal tracts and portions of the posterior column were partially demyelinated. Hematoxylinophilic granules (prelipoid deposits) were observed in both the central nervous system and the visceral organs.

The disease appears to be most closely related to amaurotic family idiocy, in spite of certain clinical and pathologic differences.

Similarities between this and other forms of heredofamilial neurologic disorder are pointed out, including the frequent involvement of the phylogenetically younger ascending and descending pathways.

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EXPERIMENTAL NEUROSES AND PSYCHOTHERAPY

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Clinical psychotherapeutic methods, once mystic, then largely empiric, have only recently begun to acquire a demonstrable psychobiologic rationale. As a contribution from the field of comparative dynamic psychology, I shall attempt to show in this report that therapeutic technics developed in the study of experimental neuroses in animals conform with certain fundamental principles of behavior, which also govern the psychotherapy of human subjects.

EXPERIMENTAL OBSERVATIONS [1]

Production of Neuroses in Animals.—By means of an automatic conditioning apparatus, cats were trained to lift the lid of a box to secure food in response to one or more signals in various sensory modalities. As a control procedure, the box was then locked, or the animal was otherwise mechanically frustrated in its food taking; under these circumstances the conditioned responses to the feeding signals were rapidly extinguished, but no other behavior abnormalities developed. If, however, the food was made freely accessible after the signal, but the act of feeding itself was rendered motivationally conflictful by administering a disturbing, although harmless, blast of air across the box at the moment of food taking, the animal rapidly acquired an "experimental neurosis," characterized by manifestations of anxiety whether it was in or out of the apparatus, hyperesthetic startle reactions, consistent "phobic" responses to the feeding signals, to space constriction or to other meaningful con-

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1. The necessary control experiments, the various characteristic behavior abnormalities constituting "the psychopathology of animal life" and the principal methods of treating experimental neuroses are recorded in a series of 16 mm. motion picture films distributed by the department of psychiatry, the University of Chicago. I have described the apparatus and technics employed in these studies in previous publications (An Automatic Apparatus for the Central Conditioning of Small Animals, J. Comp. Psychol. **28**:201, 1939; Is the Hypothalamus a Center of Emotion? Psychosom. Med. **3**:1, 1941; Psychobiologic Dynamisms in Behavior, Psychiatry **5**:341, 1942). A more detailed description and analysis of the experimental results for 212 animals over a period of seven years will be included in a monograph entitled "Behavior and Neuroses," to be published.

figurations previously associated with the conflict situation, stereotyped "compulsion" and "fixation" patterns of hiding or escape, "narcissistic" or regressive manifestations, such as excessive licking and preening, and even protracted avoidance of food and self starvation to the point of extreme cachexia.

Therapeutic Technics.—The "neurotic symptoms" just described persisted for months after only from one to four "emotionally traumatizing" experiences; nevertheless, the experimental neurosis could be diminished or abolished at any time by various experimental procedures, classifiable under the following five categories:

1. Diminution of Intensity of One of the Conflictful Drives: If a neurotic animal was manually, or even forcibly, fed just before being replaced in the conflict situation, its phobic, compulsive and anxiety reactions were significantly less marked than when its hunger was intense.

2. "Reassurance," "Persuasion" and "Suggestion": If the experimenter, by petting and gentle hand feeding, patiently retrained the neurotic animal to take food from the box, the phobic responses to the signals were gradually replaced by normal food seeking; other neurotic reactions abated, and the animal eventually became capable of withstanding even the previously phobogenic air blasts without flinching. In fact, in some animals the air blasts themselves later became positive conditional signals for feeding.

3. Environmental Press: In contrast to these therapeutic methods, the feeding inhibitions could also be disrupted through environmental manipulations, e. g., by employing a movable barrier in the cage to force the neurotic animal, at the height of its hunger, ever closer to the open food box as it became filled with delectable pellets of salmon seasoned with catnip. As the animal was thus slowly but inexorably brought nearer the locus and psychologic nidus of its conflict, its anxiety and attempts to escape at first increased in intensity; finally, however, the maximally reenforced hunger drive explosively broke through the counterpoised inhibitions, and furtive, hurried gulping of food occurred. Once the motivational impasse was broken, the feeding behavior soon became more natural; normal responses to the signals returned; the "claustrophobic" reaction to the space constriction disappeared, and the other neurotic manifestations rapidly diminished in intensity.

4. "Social Example": When a cat with active feeding responses to the signals was placed in the experimental situation with the self-starved, cringing, neurotic animal, the latter gradually began to join in the food taking, although for days thereafter this could easily be disrupted and the neurosis reactivated by exhibition of the conditional signals when

the animal was alone in the cage. This method, in fact, was the least reliable of the five with regard to the permanent dissipation of aberrant manifestations in the neurotic animal.

5. "Working Through": Finally, several animals were themselves trained to manipulate a switch which controlled both the feeding signals and the automatic deposition of food in the box. If the switch was then turned off so that the signals did not operate, the animals made no attempt to feed, but continued to depress the switch until the signals again appeared before taking food. When the animals were made neurotic by the air blast technic, they at first ignored or avoided the switch; however, most animals gradually reexplored its use with increasing confidence until they had reestablished their self-signaling and feeding patterns despite repetitions of the air blast and had thus. by trial and success activity, resolved their motivational conflict and its derived neurotic manifestations. These neurotic animals, then, "worked through" their conflict in a manner denied to others not given such manipulative control of the experimental situation.

COMMENT [1]

I have elsewhere proposed four fundamental principles of behavior, which may be briefly restated here as follows:

1. Behavior is motivated by the biologic needs of the organism.

2. Behavior is contingent on, and adaptive to, the meanings of the "objective" and "social" environment as interpreted by the individual organism.

3. Behavior relieves bodily tensions not only by direct but also by substitutive or symbolic activity.

4. When psychobiologic motivations or environmental meanings become excessively confused or conflictful, behavior likewise becomes abnormally substitutive, symbolic and biologically inefficient, that is, "neurotic" or "psychotic" in character.

These propositions are confirmed by the experimental results with animals here reported. Moreover, that similar principles underlie the infinitely more complex phenomena of clinical psychiatry and are consistent with various psychotherapeutic technics may be indicated by a brief review.

The Concept of Motivational Conflict.—This concept is explicit or implicit in almost all dynamic theories of the etiology of the neuroses. Psychoanalysis has shown that in men, as well as in animals, environmentally conditioned motivational conflicts engender anxiety, which then finds both deviated expression and partial mitigation in symbolic or substitutive behavior patterns, such as phobias, compulsions, fixations

and regressions. Similarly, clinical psychotherapeutic methods correspond in rationale with those employed experimentally as follows:

Diminution of Conflictful Bodily Needs: It is generally recognized that admission to a sanatorium, bodily rest, physical therapy, temporary isolation, proper feeding, etc., are psychotherapeutically effective largely because they conform to certain of the patient's conscious or unconscious psychobiologic needs, such as those for passivity, security or just environmental relief from excessive emotional stresses. When these needs are not symbolically gratified, or the meanings of the therapeutic efforts are psychotically misinterpreted, the procedures employed are generally of little therapeutic avail. Moreover, it is probable that many sedative and hypnotic drugs relieve anxiety not so much by specific pharmacologic action as by numbing the apperception of internal emotional tensions and conflicts. Similarly, occupational therapy and bodily exercise may serve mainly as acceptable outlets for conflictful drives and thus indirectly diminish the intensity of the latter. Conversely, in psychoanalytic technic direct sexual gratification may for a time be purposely forbidden in order that related anxieties and conflicts may become pressing and thereby more accessible to analysis.

Reassurance, Suggestion and Persuasion: In these "transference" technics, the therapeutist, like the experimenter trusted by the neurotic animal, utilizes the dependent confidence invested in him by his subject to increase the security of the latter and thus induce him to attempt solutions of emotionally conflictful life situations previously reacted to only with paralyzing anxiety or with aberrant behavioral defenses. Thus, the psychiatrist, by the use of emotionally cathectic (and thereby thaumaturgic) verbal or other manipulative symbols, may "persuade" a neurotically anorexic, vomiting patient with intensely conflictful oral needs to take food, and may even reenforce this therapy by symbolically manipulative methods, such as having a matronly nurse do the introductory spoon feeding. Unfortunately, while such therapeutic procedures may provide highly desirable symptomatic relief, they do not resolve the manifold, deeply ingrained and stoutly defended conflicts that unconsciously actuate most human neuroses. In such cases, of course, the results of short term psychotherapeutic procedures are usually neither as striking nor as lasting as those obtained in relatively stable animals made experimentally "neurotic" by a single motivational impasse produced only a comparatively short time before corrective procedures are instituted. The psychobiologic principles involved in both cases, however, may well be nearly identical.

Forced Solution: It will be recalled that with this method the animal's feeding inhibitions were overcome by forcing it mechanically into the vicinity of attractive food at the height of its hunger; once feeding occurred, the animal's anxiety and the ancillary behavioral

aberrations rapidly diminished. Empirically, it has long been recognized that direct manipulative methods may be used successfully with normally well integrated subjects within a reasonably short time after an acutely disturbing emotional trauma. For example, experience in war psychiatry has shown that an airplane pilot who, although uninjured, exhibits excessive anxiety after a crash can frequently be kept from development of a chronic and disabling neurosis by being forced, either physically or by effective press of custom and authority, to fly another plane immediately. Similarly, acute anxiety states in soldiers are often best treated in front line stations by authoritative methods of reassurance and persuasion, followed by direct return to duty as soon as possible. In the therapy of the more chronic civilian neuroses less intensive pressures must of necessity be used, if only to preserve the patient's tenuous cooperation and rapport; nevertheless, environmental manipulations and familial, economic and other reality influences can often be brought to bear not only to diminish the secondary and regressive gains of the neuroses, but to induce the patient to face his emotional problems more directly.

"Social Example" and Identification: The principle that one emulates, and thereby "identifies," with persons whose characteristics and advantages one cherishes or envies is implicit in most pedagogy and social training and is widely applicable in psychotherapy. A person raised as a devout Mohammedan who migrates to an Occidental culture, with which he then wishes to conform, will gradually lose the intensely phobic distaste for pork more appropriate to his earlier experience. Again, a rejected, withdrawn, aggressive child, placed among secure, friendly foster siblings will tend, other factors being equal, to adopt their socially more desirable characteristics in order to share their reward of parental love and security. Similarly, states of acute disabling panic in civilians subjected to bombing or other wartime dangers are often effectively controlled by giving the person so affected a specific part in a smoothly functioning team of friends and neighbors who are engaged in some purposeful defensive or offensive activity. In simpler paradigm, the starving but anxiety-ridden neurotic cat tentatively copies and eventually readopts the environmental adaptations of a cage mate which by its normal feeding responses demonstrates that such behavior is possible and biologically successful.

"Working Through": Neurotic cats given the means (electric switch) with which to test the symbolic and reality aspects of their environment (signals and feeding) gradually "work through" and eventually eliminate their neurotically inefficient patterns in a manner impossible for cats not given access to such environmental manipulations. The achievement of progressively more efficient reality relationships through exploratory selection and channeling of adaptive activity on the

part of the subject is of great psychotherapeutic importance. Thus, even in initially subjective procedures, such as psychoanalysis, the patient must later be induced to test out and apply in actual reality manipulations the newly acquired insights into his previously unconscious object and interpersonal relationships. The deeper such analytic insights, the better will be the patient's understanding of his reality symbolisms, the more frank and accurate his evaluation of his own motivations and the more effective the working through and adjustment of his emotional problems to his daily living.

Finally, it is significant that, with allowance for individual variations, a combination of all five therapeutic procedures produced the most rapid and lasting return to psychobiologically normal behavior in the neurotic animals. So, too, in human subjects effective psychotherapy often combines, first, the initial relief of excessive anxiety through the use of various procedures directed toward the diminution of motivational conflicts; second, the establishment of an effective therapeutic influence through a working identification and rapport with the psychiatrist; third, the employment of this and other interpersonal relationships to induce the patient to establish more satisfactory norms of social conduct; fourth, the use of graded amounts of reality pressure (by the physician, the patient's family, his employer and others) to force the patient to solve his emotional problems as his diminishing anxiety permits, and, finally, the provision of vocational, recreational and other operational means that make it possible for the patient to work through his reality and interpersonal maladjustments in behavior increasingly adapted to his milieu.

SUMMARY

Artificially induced motivational conflicts in animals induce "experimental neuroses," characterized by anxiety reactions, persistent inhibitions, sensory hyperesthesias, phobias, compulsions and other aberrant behavior patterns that correspond to those in human psychopathology. These neurotic manifestations are diminished or abolished by various therapeutic technics which (1) mitigate the intensity of the motivational conflict, (2) decrease the resultant anxiety, (3) force a solution by environmental pressure, (4) furnish a "social example" of more satisfactory behavior or (5) provide the animal with manipulative means to "work through" the emotionally conflictful reality situation. These observations are consistent with certain psychobiologic principles applicable alike to comparative dynamic psychology, to semeiotic psychiatry and to clinical psychotherapeutic technics.

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CONSTITUTIONAL DIFFERENCES BETWEEN DETERIORATED AND NONDETERIORATED PATIENTS WITH EPILEPSY

V. CAPILLARIES OF THE FINGER NAIL FOLD

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Because their material was studied in institutions for the insane, the majority of writers on epilepsy have expressed the opinion that this disorder inevitably leads to mental deterioration. This view was challenged by one of us (H. A. P.) [1] in 1932, in a study made on epileptic patients seen in private, extramural practice. In that study attention was directed to the fact that only 6.5 per cent of 304 such epileptic patients presented mental changes characteristic of epileptic deterioration after a suitable lapse of time. The remaining patients in this series retained normal mental health and suffered no impairment in their ability to work at their various vocations. We have become convinced that the disorder known as "idiopathic epilepsy" is of two types: In one variety mental deterioration occurs, and in the other it does not.

In addition to the mental status, certain differences between the mentally deteriorated and the nondeteriorated epileptic patients have been studied by us. In one communication [2] it was shown that the hereditary background of the deteriorated patient is more heavily loaded with neuropathic disturbances than that of the nondeteriorated patient. The onset of the seizures was found [3] to occur earlier in life among the deteriorated epileptic patients than among the nondeteriorated ones, and the deterio-

† Dr. Paskind died on March 24, 1942.

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1. Paskind, H. A.: Extramural Patients with Epilepsy, with Special Reference to the Frequent Absence of Deterioration, Arch. Neurol. & Psychiat. **28**: 370 (Aug.) 1932.

2. Paskind, H. A., and Brown, M.: Hereditary Factors in Epilepsy: Differences Between Deteriorated and Nondeteriorated Patients, J. A. M. A. **108**: 1599 (May 8) 1937.

3. Paskind, H. A., and Brown, M.: Age of Onset of Epilepsy: Differences Between Deteriorated and Non-Deteriorated Patients, Am. J. Psychiat. **96**:59 (July) 1939.

rated patients were shown [4] to have a greater number of seizures than the nondeteriorated ones.

For several years we have been studying differences of a constitutional, or inborn, nature between these two groups of patients. A greater profusion of anatomic anomalies (stigmas of degeneracy) was demonstrated [5] among the deteriorated than among the nondeteriorated epileptic patients. In other studies we reported significant differences in the body habitus,[6] the dactylographic patterns (finger prints) [7] and the character of the handwriting.[8] These studies suggest that deteriorated and nondeteriorated epileptic patients differ from each other before birth, since the differences described are inborn, or genotypic, in character.

The present communication is concerned with another constitutional mark, the capillaries of the finger nail fold.

Since 1911, when Lombard [9] first visualized the capillaries in the fold of skin at the base of the finger nail in the living patient, there have been numerous studies on the morphology and development of these capillaries. The majority of authors dealing with capillaries of the nail fold have come to the conclusion that their formation, which occurs during the first few years of life, is controlled by constitutional factors and that thereafter the morphologic character of the capillaries remains unaltered except for the changes induced by growth and local trauma. This was the opinion expressed by Crawford,[10] Hagen,[11] Jaensch,[12] von

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12. Jaensch, W.: Die Hautkapillarmikroskopie, Halle, Carl Marhold, 1929.

4. Paskind, H. A., and Brown, M.: Frequency of Seizures in Epilepsy: Differences Between Deteriorated and Non-Deteriorated Patients, Am. J. Psychiat. **96**:65 (July) 1939.

5. Paskind, H. A., and Brown, M.: Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy: I. Stigmas of Degeneracy, Arch. Neurol. & Psychiat. **36**:1037 (Nov.) 1936.

6. Paskind, H. A., and Brown, M.: Constitutional Differences Between Deteriorated and Non-Deteriorated Patients with Epilepsy: II. Anthropometric Measurements, Am. J. Psychiat. **95**:901 (Jan.) 1939.

7. Brown, M., and Paskind, H. A.: Constitutional Differences Between Deteriorated and Non-Deteriorated Patients with Epilepsy: III. Dactylographic Studies, J. Nerv. & Ment. Dis. **92**:579 (Nov.) 1940.

8. Paskind, H. A., and Brown, M.: Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy: IV. The Handwriting, Arch. Neurol. & Psychiat. **44**:507 (Sept.) 1940.

9. Lombard, W. P.: Der Blutdruck in den Kapillaren und Venen der menschlichen Haut, Zentralbl. f. Physiol. **25**:157, 1911.

10. Crawford, J. M.: Human Capillaries: Observations of the Capillary Circulation in Normal Subjects, J. Clin. Investigation **2**:351, 1926.

11. Hagen, W.: Periodische konstitutionelle und pathologische Schwankungen im Verhalten der Blutcapillaren, Virchows Arch. f. path. Anat. **234**:504, 1922.

Lederer,[13] Stefko,[14] Ubenauf [15] and Leader.[16] Delbruck,[17] Gänsslen [18] and Fischer,[19] however, expressed disagreement with this view. Strong proof of the overwhelming importance of constitutional factors in determining the morphologic pattern of the capillary loops is offered by the studies of Doxiades and Uhse,[20] Lehmann and Hartlieb,[21] Mayer-List and Hubner [22] and Schiller.[23] These authors have shown that the capillaries of the nail fold of identical twins bear a much closer resemblance to each other than those of nonidentical twins.

From the work of the authors cited we believe it safe to accept the morphology of the capillaries in the nail fold as a constitutional mark. We have, therefore, compared the capillaries of the nail fold of deteriorated epileptic patients with those of nondeteriorated persons similarly afflicted in order to determine whether differences here might indicate differences in constitution.

The capillaries of the nail fold were investigated in epileptic patients by Euzière, Lafon and Toye,[24] Kreyenberg,[25] Brahm,[26] Mari,[27]

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13. von Lederer, E.: Die Bedeutungen Capillarmikroskopie in der Prognose und Therapie der Oligophrenie, Monatschr. f. Kinderh. **58**:429, 1933.

14. Stefko, W.: Die Entwicklung der Hautkapillaren in Kindesalter, Kinderärztl. Praxis **2**:468, 1931.

15. Ubenauf, K.: Die konstitutionspathologische Bedeutung der Capillarhemmung, Arch. f. Psychiat. **100**:700, 1933.

16. Leader, S. D.: Capillary Microscopy in Children, Am. J. Dis. Child. **44**: 403 (Aug.) 1932.

17 Delbruck, H.: Archcapillaren und Schwachsinn, Arch. f. Psychiat. **81**: 606, 1927.

18. Gänsslen, M.: Der Einfluss veränderter Nahrung auf den periphersten Gefässabschnitt, Klin. Wchnschr. **6**:786, 1927.

19. Fischer, L.: Der allgemeine und ortliche Veränderungen am Capillarsystem, Klin. Wchnschr. **2**:1337, 1931.

20. Doxiades, L., and Uhse, W.: Neue klinische Befunde am Zwillingen, Monatschr. f. Kinderh. **62**:196, 1935.

21. Lehmann, W., and Hartlieb, J.: Capillaren bei Zwillingen, Ztschr. f. menschl. Vererbungs- u. Konstitutionslehre **21**:271, 1937.

22. Mayer-List, R., and Hubner, F.: Die Capillarmikroskopie in ihrer Bedeutung zur Zwillingsforschung, ein Beitrag zur idiotypischen Bedingtheit des vegetativen Gefäss-syndrome, München. med. Wchnschr. **72**:2185, 1925.

23. Schiller, M.: Zwillingsproblem dargestellt auf Grund von Untersuchungen an Stuttgarten Zwillingen, Ztschr. f. menschl. Vererbungs- u. Konstitutionslehre **20**:284, 1937.

24. Euzière, J.; Lafon, R., and Toye, F. P.: Tares mentales et morphologie des vaisseaux capillaires cutanés, Arch. Soc. de sc. méd. et biol. de Montpellier **16**: 401, 1935.

25. Kreyenberg, G.: Capillaren und Schwachsinn, Arch. f. Psychiat. **88**:545, 1929.

26. Brahm, A. M.: Capillarmikroskopische Untersuchungen bei genuinen Epilepsie, Deutsche med. Wchnschr. **55**:183, 1929.

27. Mari, A.: La ricercha capillariscopica in psichiatria, Riv. di pat. nerv. **40**: 588, 1932.

Milewski and Wilczowski,[28] Schnidtmann,[29] Schryver-Hertzberger[30] and Leader.[16] Altogether, 537 patients were studied by these authors. Although their methods of describing or classifying abnormalities in capillary morphology varied considerably, they expressed the unanimous opinion that bizarre capillaries and abnormalities in the development of the capillary loops are unusually frequent among epileptic patients. From 33 to 87 per cent of the epileptic patients whom they studied were found to have abnormal capillaries. The value of these studies suffers greatly from the fact that patients with primary congenital mental deficiency, who are not truly epileptic, were often included in their observations. Furthermore, none of the epileptic patients studied by these authors were said to be without mental changes.

We studied the capillaries of the nail fold in 78 deteriorated patients with epilepsy who had been committed to the Elgin, Chicago and Dixon State Hospitals and in 100 nondeteriorated patients from the outpatient clinic of Northwestern University Medical School and Rush Medical College. Of the institutional patients, 38 were males and 40 females; 58 of the extramural patients were males and 42 females. The ages of the patients were similar in the two groups, most of the patients being from 20 to 40 years of age. In order to allow time for deterioration to occur, no patient was accepted for the group not showing deterioration unless seizures had been present for at least four years; many of these patients had had seizures for decades. In both groups we were careful to exclude persons with defective mental development; in some instances this was done with the aid of psychometric tests and in others by a study of the educational and vocational experiences of the patient. No patient was accepted who had signs of focal neurologic disorder.

The skin fold at the base of the nail on the fourth (ring) finger of the right hand was studied in all subjects. Fingers which had been traumatized were not used in the present study. Photomicrographs were made of all portions of the nail fold in every subject, the magnification used being 40 diameters. From four to eight exposures were made in each case. The morphologic pattern of the capillary loop was studied from the unretouched negatives of the photographs, not from the patient directly.

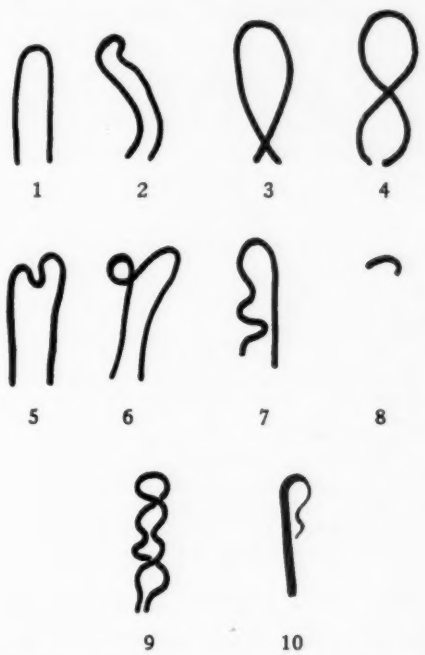
From a study of the forms of the capillary loops it is possible to classify them into ten general types. The classification is based on the morphologic pattern of the loop itself, not on its position or the character

28. Milewski, and Wilczowski, E.: Capillarskopische Untersuchungen bei Epileptikern, Roczn. pschjatr. **10**:79, 1929.

29. Schnidtmann, M.: Nagelfalzcapillaren und Schwachsinn, Arch. f. Psychiat. **94**:470, 1931.

30. Schryver-Hertzberger, S.: Ueber das Capillarbild bei Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:261, 1932.

of the blood flow within it. The figure shows the various kinds of capillary loops encountered in the patients studied. Type 1, which by many authors is regarded as the normal variety of capillary loop in the nail fold, resembles a hairpin. Both its ascending and its descending limb are well developed and straight, and they are of equal size. Type 2 resembles type 1 except that both its ascending and its descending limb are slightly tortuous, though parallel to each other. Capillaries belonging to type 3 form a simple loop, which is shaped like the written letter *l*. A figure of eight is formed by capillaries belonging to type 4. In type 5 both the ascending and the descending limb of the



Types of capillary loops encountered in the nail folds of deteriorated and of nondeteriorated patients with epilepsy.

loop are straight, but the upper portion is slightly tortuous. There is a great deal of resemblance between types 5 and 6; in the latter the upper portion of the capillary loop is more tortuous than that in type 5, and a secondary L-shaped loop is present. Type 7 represents a form in which one limb of the capillary loop is straight and the other tortuous. Under type 8 are included capillary loops which are rudimentary; they are difficult to see and appear to be partially developed. Capillary loops belonging to type 9 include those in which both the ascending and the descending limb are tortuous; capillaries which are bizarre in

appearance and do not fit into the other categories are included in this group. Under type 10 are placed all capillary loops in which one limb is much larger than the other. Only those capillary loops which were seen clearly were included in the present study.

In the table may be seen the frequency with which the various types of capillary loops were encountered in the finger nail folds of the deteriorated and of the nondeteriorated patients with epilepsy. Study of this table shows several interesting and statistically significant differences between the two groups of subjects. The simple hairpin variety of capillary loop (type 1) occurs almost three times as frequently in the nail folds of the extramural subjects as in the nail folds of the

Frequency of Occurrence of Various Types of Capillary Loops in the Nail Folds of Deteriorated and Nondeteriorated Patients with Epilepsy

	Deteriorated Patients			Nondeteriorated Patients		
	Male	Female	Male and Female	Male	Female	Male and Female
Number of capillaries observed.....	1,272	1,632	2,904	1,273	1,638	2,911
Number of patients studied.....	38	40	78	58	42	100
Types of capillary loops, percentage						
1.....	25.6 ± 0.82	18.3 ± 0.64	21.5 ± 0.51	57.3 ± 0.77	63.5 ± 0.80	60.1 ± 0.56
2.....	2.6 ± 0.30	3.4 ± 0.30	3.1 ± 0.22	2.1 ± 0.22	3.7 ± 0.31	2.8 ± 0.19
3.....	13.2 ± 0.69	13.4 ± 0.57	13.3 ± 0.42	15.2 ± 0.56	12.7 ± 0.55	14.0 ± 0.39
4.....	10.8 ± 0.62	8.5 ± 0.46	9.5 ± 0.37	11.1 ± 0.49	7.1 ± 0.43	9.3 ± 0.33
5.....	7.6 ± 0.52	5.0 ± 0.36	6.1 ± 0.30	1.9 ± 0.21	0.7 ± 0.14	1.4 ± 0.13
6.....	3.4 ± 0.34	1.5 ± 0.20	2.3 ± 0.19	1.6 ± 0.20	1.0 ± 0.17	1.3 ± 0.13
7.....	2.1 ± 0.27	1.3 ± 0.19	1.6 ± 0.16	0.6 ± 0.12	1.0 ± 0.17	0.8 ± 0.10
8.....	0.6 ± 0.15	1.6 ± 0.21	1.2 ± 0.14	0.6 ± 0.12	1.2 ± 0.18	0.9 ± 0.11
9.....	26.9 ± 0.84	38.8 ± 0.81	33.6 ± 0.59	7.3 ± 0.40	6.6 ± 0.41	7.0 ± 0.29
10.....	7.2 ± 0.49	8.2 ± 0.46	7.8 ± 0.34	2.3 ± 0.23	2.5 ± 0.26	2.4 ± 0.17

deteriorated patients. Thus, of 2,911 capillary loops visualized in the nondeteriorated patients, 60.1 per cent were of type 1; for the 2,904 capillary loops from deteriorated subjects the corresponding value was only 21.5 per cent. The same kind of difference was found when the male or the female subjects were studied separately. Types 2, 3, 4 and 6 occurred with almost equal frequency in the two groups of subjects. Capillaries classified as type 5 were significantly more frequent among female institutional epileptic patients than among female extramural patients. The same was true for capillaries of type 7. Capillary loops belonging to types 8, 9 and 10 occurred more frequently in the deteriorated subjects than in the nondeteriorated ones. This difference was also significant statistically, and it was found to remain so when the men and women of the two groups are compared with each other separately.

From the foregoing study of the morphology of the capillaries of the nail fold of 78 deteriorated epileptic patients and 100 epileptic patients without deterioration it may be concluded that the following significant differences between the two groups exist:

1. The so-called normal, or simple hairpin-shaped, capillary loop occurs more frequently in the nail folds of nondeteriorated subjects than in those of the mentally deteriorated ones.

2. Rudimentary or poorly developed capillary loops are found in a larger proportion of institutional patients than of nondeteriorated ones.

3. Tortuous and bizarre capillaries are significantly more frequent among deteriorated subjects than among nondeteriorated ones.

4. In the mentally deteriorated epileptic patients the incidence of capillary loops in which one limb is much more fully developed than the other is greater than in the mentally normal epileptic patients.

From these observations it is concluded that further evidence has been adduced to support the view that there are constitutional, or inborn, differences between the deteriorated and the nondeteriorated patient with epilepsy.

INTRACRANIAL DERMOID AND EPIDERMOID TUMORS

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MEDICAL CORPS, ARMY OF THE UNITED STATES

In a recent survey of the reported cases of intracranial dermoid tumors, Broager [1] stated that 62 verified cases are on record and that, of these, operation was performed in only 19. At the same time he reported that the larger series of dermoid and epidermoid tumors indicate that the latter are approximately four times as common as the former. In view of these facts, it seems important to put on record 4 cases of intracranial dermoid tumors and 1 case of epidermoid tumor (an exact reversal of Broager's ratio), in all of which operation was successfully performed, selected from a total of well over 700 verified cases of intracranial tumors.

It is not the purpose of this paper to review the statistics on all reported cases of intracranial dermoid and epidermoid tumors or to deal widely with the histology, clinical symptoms and surgical problems of such tumors. These matters have been considered in detail by Bostroem,[2] Brock and Klenke,[3] Sweet [4] and Broager.[1] It is of considerable interest to discover that in all of the reported series the epidermoids far outnumber the dermoids. In Cushing's [5] total series of 2,023 verified intracranial tumors, reported on in 1932, there were 12 epidermoids and 3 dermoids. Broager's series of 759 verified tumors in Rigshospitalet in Copenhagen, Denmark, included 9 epidermoids and 2 dermoids. Courville and Kimball,[6] in a series of 529 intracranial tumors verified at

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1. Broager, B.: Acta chir. Scandinav. **85**:51, 1941.
2. Bostroem, M.: Zentralbl. f. allg. Path. u. path. Anat. **8**:1, 1897.
3. Brock, S., and Klenke, D. A.: Bull. Neurol. Inst. New York **1**:328, 1931.
4. Sweet, W. H.: Dis. Nerv. System **1**:228, 1940.
5. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1932.
6. Courville, C. B., and Kimball, T. S.: Bull. Los Angeles Neurol. Soc. **1**:84, 1936.

autopsy, found but 1 intracranial dermoid, and "that a small one discovered incidentally in the course of a routine examination of the intracranial contents. Love and Kernohan [7] reported 15 instances of such tumors from the files of the Mayo Clinic; of these tumors, 10 were epidermoids and 5 dermoids (3 intracranial and intradural, 1 extracranial and 1 intraspinal). In a discussion on that paper, Sachs stated that at that time he had had 6 epidermoids and no dermoids, and Spurling reported that he had had 2 epidermoids and no dermoids. Other equally interesting reports confirm the fact that, granted that all histologic diagnoses were correct, epidermoids usually far outnumber dermoids in their frequency of occurrence in authenticated series of intracranial tumors.

Clarification is needed in the definition of epidermoid, dermoid and teratomatous tumors. Most authors agree that, with the histologic appearance of these tumors as a source of definition, the epidermoid is a benign tumor, congenital in origin, and consists only of epidermoid cells and their products of disintegration. By the same method, the dermoid is a benign tumor, congenital in origin, and may contain representative structures from a part or all of the constituents of the entire dermis. That is, a dermoid tumor may contain hair, sebaceous and sweat glands, teeth, nails and skin. Teratoma is a tumor of congenital origin; it may be either benign or malignant and contains representative tissues from all three embryonic germ layers.

The definition of an epidermoid seems simple and reliable enough. Examination of such tumors from many different clinics shows them to vary little or not at all in their microscopic structure. The capsule is a thin, friable membrane, consisting only of stratified, desquamating epithelium, such as one sees on the surface of any skin. The main mass of the tumor is composed of the products of decomposition of these epithelial cells, and while much of it is amorphous and not particularly definable, part of it is crystalline cholesterol. Crumbs of the tumor, looking much like dried bits of cottage cheese, are seen to fluoresce in ultraviolet light, and fresh smears show masses of typical cholesterol crystals, the outlines of which are made more distinct by the addition of a drop of cresyl violet stain to the fresh preparation. The term "cholesteatoma" is frequently used interchangeably with "epidermoid" in naming such a tumor. This is an undesirable and confusing practice. If "cholesteatoma" were reserved for those tumor-like masses that are actually granulomas resulting from chronic infection and that are frequently seen in various portions of the upper respiratory tract and of

7. Love, J. G., and Kernohan, J. W.: Dermoid and Epidermoid Tumors (Cholesteatomas) of Central Nervous System, J. A. M. A. **107**:1876 (Dec. 5) 1936.

the temporal bone, it would prevent confusion with the diagnosis of true epidermoid tumor.

For all practical as well as theoretic purposes, it would be best to reserve the term "dermoid" for those tumors which show tissues arising only from the ectoderm, such as epidermis, hair, nails, teeth and sebaceous and sweat glands. As a matter of fact, in most reports these tissues form the contents of the tumor called dermoid. In addition to these strictly integumentary structures, nerve tissue has been observed in some dermoid tumors, this inclusion being permissible if one extends the definition of dermoid to include embryonic representatives of the entire ectoderm, instead merely of the dermis. But actual difficulty does arise when a tumor, mainly dermoid in appearance, contains also some muscle fibers, bits of cartilage or bone or strands of fibrous connective tissue. Here, then, is a tumor representing two embryonic germ layers, and by original definition it is neither dermoid nor teratoma. It is of such frequent occurrence to find these mesodermal elements reported as the contents of a histologically verified and supposedly "dermoid" tumor that one wonders whether, because of this frequent histologic observation, the dermoid should be renamed in some such way as to include tissues from both the ectoderm and the mesoderm. This difficulty has also been noted by Sweet, who suggested the use of the term "teratoid" for a tumor containing elements from two germ layers. By use of the classification of "teratoid tumor" the term "dermoid," time honored and firmly established, could be preserved for the tumor containing only ectodermal derivatives. Sweet suggested the term "teratoid" for any tumor containing representatives from any two of the three primary germ layers. The adoption of this term, definition and classification is desirable, for it bridges the gap between the true, or simple, dermoid of purely ectodermal origin and the more complex tumors inclining to the teratomatous side of the scale.

The definition of teratoma is accurate and practical. Its rarity and its frequent tendency to undergo malignant change are two important characteristics.

The problem of why epidermoids and dermoids arise where they do intracranially brings out many interesting facts, theories and speculations. Courville and Kimball[6] stated:

> New growths of embryonic origin within the cranium may be divided into two groups. In the first group, the tumor arises from residual cells of some specific structure such as the craniopharyngeal canal (craniopharyngioma) or the notochord (chordoma) and is always found in the region of the parent structure. Tumors of the second group apparently arise from "cell rests" derived from the original tissue layers and are, therefore, confined to no special locality, although, to be sure, they may show a predilection for certain regions. This group is made

up of three types of tumors, all of which are relatively rare—epidermoids or cholesteatomas, dermoids and teratomas.

Bostroem [2] stated that early amniotic adhesions might cause a local isolation, or nest, of cells, producing an anlage for an epidermoid or dermoid, the age of the anlage determining which of these two tumors would result (up to the third week, the dermoid; fourth or fifth week, the epidermoid). Arey [8] pointed out that dermoids, resulting from embryonic epidermal inclusions, are not infrequent along the line of fusion of various embryonic structures, such as the branchial grooves, and any place along the middorsal or the midventral body wall. Certainly, intracranial dermoids are most frequently seen in the midline, and in that position may involve the skin, the skull and the dura mater. Furthermore, the high incidence of their location below the tentorium should be explainable. Gray,[9] citing Bland-Sutton, stated that early in embryonic life the dura mater and the skin are in actual contact. Later, the developing skull normally intervenes between the dura mater and the skin, but if such a separation is incomplete, due, for example, to a defect in bone development, then the dura and the skin may adhere to one another. Such a site of adherence may act as a tumor anlage. Also when the dura mater invaginates to form the tentorium cerebelli, a fold of skin may be caught in the dural folds, again inviting the development of a local tumor. Courville and Kimball expressed the belief that there must be some real reason for the high incidence of midline cerebellar dermoids and that "since meningoceles and encephaloceles may also be found in this situation, it is possible that dermoids may also have an embryonic basis in some sort of malformation, a disturbance of cellular rather than of structural arrangement." Love and Kernohan considered the possibility of trauma as a factor in the production of such tumors. Remnants of epidermal tissue could be carried into the deep layers of the scalp, or even between the inner and the outer table of the skull, such remnants being potential sites of tumor growth. Broager made some interesting observations on the pathogenesis of epidermoid and dermoid tumors. He stated the belief that the intracranial dermoid is of an earlier embryonic origin than the epidermoid and that the localization of the tumor depends entirely on the position of the tumor anlage in relation to the medullary sulcus. He stated:

If the anlage lies within the dorsal border of the sulcus, the tumour will be localized in connection with the ventricular system; if the anlage lies in a place corresponding to the border, the tumour will be localized in or near the median line, whether it be infra-tentorially or quite anteriorly round the lamina terminalis which corresponds to the anterior neuropore, the ultimate point of closure of the

8. Arey, L. B.: Developmental Anatomy, Philadelphia, W. B. Saunders Company, 1926.

9. Gray, R. C.: Minnesota Med. **39**:530, 1939.

medullary tube; finally, if the anlage is lying more laterally towards the neural crest, the tumour may be localized laterally, on the base, in the cleft of Sylvius or on the convexity.

He also pointed out that unless a dermoid tumor lies subdurally or epidurally, it will usually be found to communicate in some place with either the pia or the ependyma. The epidermoid is most frequently seen in the cerebellopontile angle, where it simulates closely the acoustic neurinoma in clinical signs. The dermoid is rarely found in that location, and why that site seems reserved for the epidermoid is not explained by Broager.

Epidermoid and dermoid tumors situated intracranially are usually amenable to surgical treatment. Such tumors as those reported on by Gray, however, lying deep within the cerebrum and extending into either lateral ventricle, are beyond the scope of surgery. Frequently a dermoid may become infected, with resulting terminal meningitis. Or it may rupture spontaneously and spread its contents throughout the cerebrospinal fluid system, a dangerous complication but not necessarily a fatal one. Such a rupture produces a severe leptomeningeal reaction, and this, together with the actual mechanical barrier formed by the lipoid material and cellular masses, may cause blocking of the cerebrospinal fluid circulation and resultant sudden hydrocephalus. The dermoid frequently ruptures during surgical removal, for the capsule is not necessarily composed of thickened, skinlike tissue. In fact, most of the wall may be, and usually is, essentially epidermal, exactly like that of the epidermoid. The contents of a dermoid are usually lumpy masses and viscid fluid; hair may be absent or may be present in amounts from a few fine strands to matted masses. All this material is easily recoverable even though the tumor breaks up during removal. Removal of the epidermoid piecemeal is usually necessitated by rupture of the filmy, delicate capsule. Bailey, Buchanan and Bucy [10] pointed out that though the tumor is easily removed because of its complete avascularity, it tends to recur, since during the surgical extirpation a few fragments of the friable mass almost invariably escape and any such particle is another tumor anlage wherever it may settle.

Because of the comparative rarity of intracranial epidermoid and dermoid tumors, and because of the stimulation which consideration of their pathogenesis brings about, the histories of the following 5 cases are given in condensed form.

REPORTS OF CASES

CASE 1.—E. K., a single woman aged 21, began to experience early morning headache one year before coming under observation. At first the headaches were

10. Bailey, P.; Buchanan, D. M., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

supraorbital and suboccipital, later becoming constant and more or less generalized. Eventually they were accompanied by vomiting without nausea, but shortly before her admission to the hospital the vomiting ceased. For the previous six months she had noticed increasing numbness of the right side of her face, and for two months, gradual failure in visual acuity. In walking she found it difficult to maintain good balance, and she inclined to stagger toward the right. There was no history of trauma to the head.

On examination she was found to have high grade bilateral papilledema and visual acuity was greatly decreased, but there was no defect in the visual fields. The right corneal reflex was absent; the right side of the face and tongue showed decided diminution of sensation to pain but not to touch, and the right side of the face and palate did not move as well as did the left. The gait was ataxic, but she could perform accurately the finger to nose and heel to knee tests. There was no nystagmus or alteration in the movements of the extraocular muscles. The deep tendon reflexes of the right upper extremity were moderately diminished as compared with those of the left, but they were equal in the lower extremities. All abdominal reflexes were present, and there were no pathologic plantar reflexes. No difficulty in speech or swallowing was noted. Lying exactly over the external occipital protuberance there was a soft, fatty nodule the size of the tip of a finger, and on its apex was a small, dark red papule. This mass was tender when palpated and had been present since birth.

Roentgenograms of the skull showed prominent convolutional impressions. The sella was fairly large, and there was extensive thinning of the posterior clinoid processes. It was typically a sella which had undergone changes as a result of intracranial pressure originating outside the structure itself. The spinal fluid, which was under moderately increased pressure, contained but 6 cells per cubic millimeter and was without other significant characteristics.

The mass over the suboccipital ridge suggested an old meningocele, but the presence of an underlying congenital tumor was not excluded. The patient underwent operation on Aug. 28, 1931. Exactly in the midline between the two cerebellar hemispheres and occupying entirely the usual site of the cisterna magna was a dark greenish blue mass overlying the vermis and extending through the foramen magnum. The mass was contained within a limiting thick, hypertrophic arachnoid membrane and could be wiped away from the surrounding structures with moist cotton sponges. The removal was accomplished from below upward, until the tumor was seen to end in a necklike extension leading from the tentorium to the soft mass in the midline of the scalp. This extension, as well as the subgaleal mass on the scalp, was filled with a cheesy green material and a mass of matted blond hair. The entire tumor was removed, and the patient made an entirely uneventful recovery.

The specimen contained much fine hair, flakes of calcified material, coarse and granular cheesy, amorphous material, masses of epithelial cells in all stages of disintegration and a large amount of thick, brown, viscid, noncellular material, which hardened to a consistency of hard rubber in a 10 per cent concentration of solution of formaldehyde U. S. P. The diagnosis was dermoid (teratoid) tumor (figs. 1 and 2).

CASE 2.—L. M., a single woman aged 32, a deaf-mute, was brought to the hospital by ambulance in a comatose state. For a year and a half she had suffered from headache, at first localized to the back of the head and upper cervical region,

but of late becoming generalized. On three occasions she had lost consciousness during the height of a severe bout of headache. For a year she had suffered increasing difficulty in walking, until at last, for one week, she had been completely unable to walk, not because of weakness but because of complete loss of balance. She had had sudden attacks of nausea and vomiting for six months, difficulty in swallowing for four months, sudden attacks of vertigo, especially on change of position, for three months and double vision for one month prior to admission to the hospital. She had lost a great deal of weight, and her disposition had become one of fear and great concern. In fact, six months before she came under observation she had been a patient in another hospital, where the diagnosis of "hysteria" was made. In spite of a feeling of swelling and numbness in her tongue, she had an enormous appetite and ate with relish. There was no history of injury to the head.

The patient was found to have an extreme degree of papilledema on both sides, the elevation being recorded as high as 6 D. There were multiple retinal hemor-

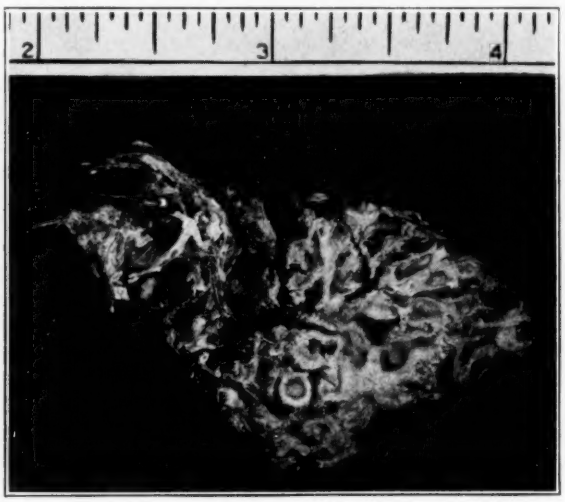

Fig. 1.—Dermoid (teratoid) tumor, total specimen. Note the masses of fine hair, the flakes of calcified material and the principal mass of amorphous tissue debris.

rhages but no defect in the visual fields. She complained of diplopia, but tests showed that all extraocular muscle movements were well performed except that convergence was poorly done. When she looked to either side there was marked nystagmus, with the quick component to the side of the gaze. Corneal and facial sensation to pain and touch was intact. There was obvious weakness of the muscles of the left side of the face, and the muscles of the pharynx and palate contracted poorly. When the patient was placed in the upright position she promptly fell backward and to the right. She was ataxic in all extremities, but testing revealed that she was more so on the left than on the right. There were no reflex changes of any nature and no pathologic reflexes, and responses to sensory tests were normal throughout.

Roentgenograms of the skull revealed nothing of significance except the presence of fairly prominent convolutional impressions.

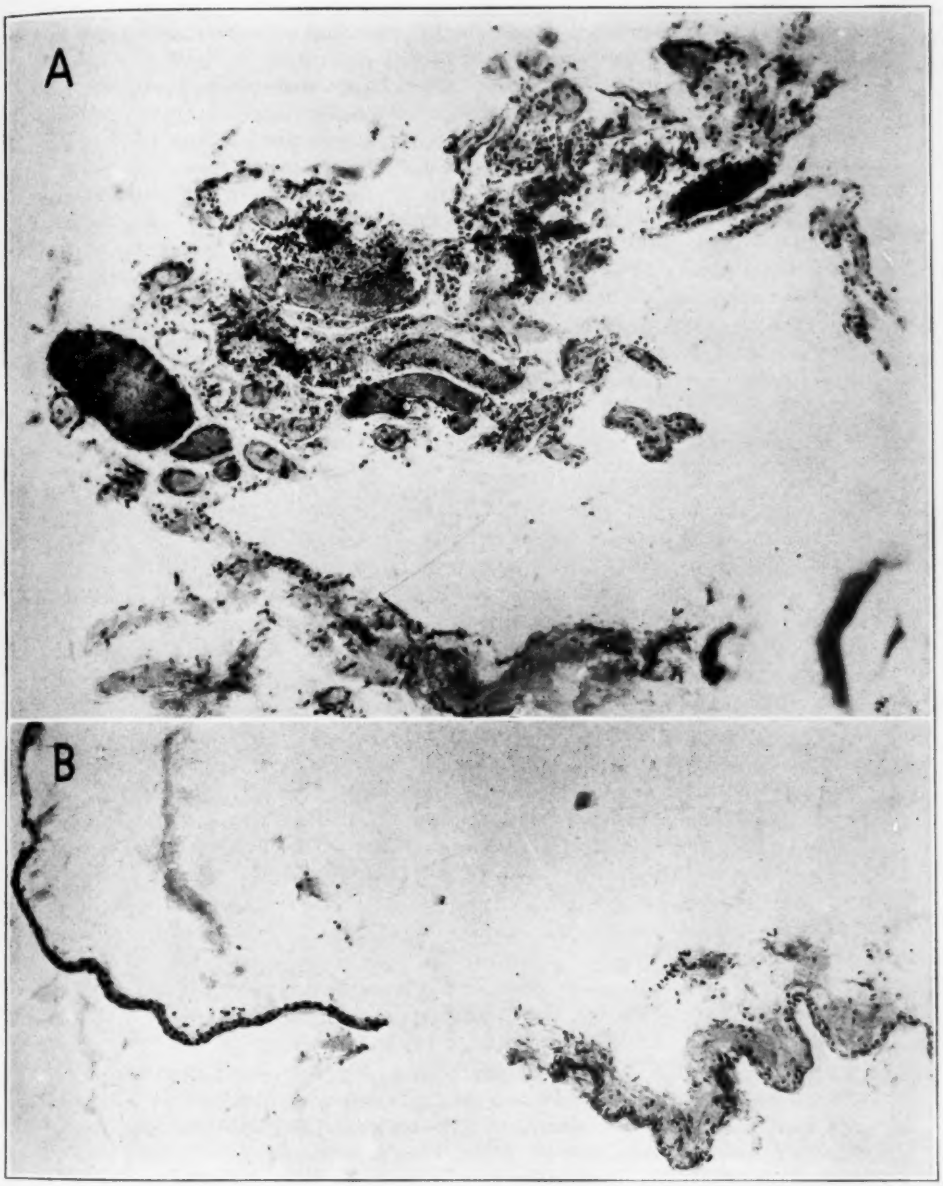

Fig. 2.—*A*, section of a dermoid tumor. Thin-walled blood vessels, coils and masses of simple epithelial cells and isolated, desquamated epithelial cells are the only stained structures. The viscid, heavy fluid which this tumor contained was free of cells and did not stain.

B, wall of a dermoid cyst. This delicate membrane is composed of epithelial cells arranged in from one to three layers. The wall of this cyst may be compared with that of an epidermoid tumor, as shown in figure 4.

Hematoxylin and eosin; × 75.

A bilateral suboccipital craniectomy was performed on July 7, 1933, and a large greenish cyst was observed to overlie the left cerebellar hemisphere and extend to the midline. During separation from the cerebellar cortex the wall of the cyst broke, with freeing of a thick, brown, tenacious material, which flowed slowly. When this material was removed the bottom of the cavity was observed to contain large, yellow, granular masses, which had the gross appearance of cholesterol crystals. When this material was removed a mass of tangled hair was seen in the depths of the cavity. When, at last, all the contents were removed, the cavity was perfectly clean, and cerebrospinal fluid once more circulated in the posterior cranial fossa. The cyst did not extend into the vermis and did not touch the tentorium. The cisterna magna was pushed to the right but was intact, and the right cerebellar hemisphere was in no way invaded. No definite point of origin for the tumor could be determined. The diagnosis was dermoid cyst.

The patient was discharged from the hospital on July 23. She walked fairly well, though with some residual ataxia, and the nystagmus had disappeared, together with her headache. Two months later the papilledema had completely disappeared, and she walked without any loss of balance and considered herself well in every way.

Case 3.—O. M., a woman aged 27, single, a bookkeeper, entered the hospital complaining of persistent occipital headache, which had been present for nine months. This discomfort was invariably worse in the afternoon; it was made worse by straining or jarring, and at no time was the headache accompanied by nausea or vomiting. One month before admission she began to notice blurring of vision, and at the same time her headache was usually accompanied by flickering, dancing lights before her eyes. Three weeks before admission she suddenly became "blind" for a minute or so while at work.

The patient was cheerful, cooperative and intelligent and appeared in good physical condition except for the complaints mentioned. Examination revealed pronounced bilateral papilledema, but no defect in the fields of vision. All extraocular muscle movements were well performed, and there was no nystagmus or diplopia. Slight diminution of touch sensation was present over the right side of the face, and there were slight but definite signs of weakness of the muscles of expression on the left side of the face. There was no difficulty of speech or swallowing and no change in the action of the palate or the muscles of the tongue. The patient was not ataxic in any extremity, and her station and gait were entirely normal. The deep and superficial reflexes were present and equal on the two sides, and there were no pathologic reflexes. Complete and repeated testing failed to elicit any further objective signs of neurologic change.

On Sept. 19, 1938, ventriculographic examination disclosed rather pronounced internal, symmetric hydrocephalus, the third ventricle lying directly in the midline. The fourth ventricle was not visualized. The ventricular fluid contained 25 lymphocytes per cubic millimeter, and the total protein content was 16.2 mg. per hundred cubic centimeters. No significant bony changes in the skull were discovered.

On September 23 a bilateral suboccipital craniectomy was performed, and when the occipital sinus was ligated there was a sudden escape of thick, green, sticky material from under the dura mater. When the dural flaps were turned back a cyst, lying directly in the midline, was observed to extend from high between the cerebellar hemispheres, but not reaching the tentorium, to and through the foramen magnum. It was globoid above and separated the hemispheres, but below, where it separated and compressed the cerebellar tonsils, it narrowed considerably into a

tonguelike structure. The tumor was soft and friable, but it stayed fairly well contained within its thin wall and was eventually wiped completely free of all attached brain tissue. It contained much thick, greenish brown, viscid fluid; chips of a hard white substance much like bone; crumbly, yellow masses which looked like cholesterol, and many strands of fine hair. Though the brain tissue was in no place invaded, the vermis, as such, could not be identified. The histologic diagnosis was dermoid (teratoid) tumor. The gross and microscopic appearance of this tumor was much the same as that of the tumor in case 1.

The patient was discharged from the hospital two weeks after her operation, and her postoperative course was entirely uneventful. She returned to work two

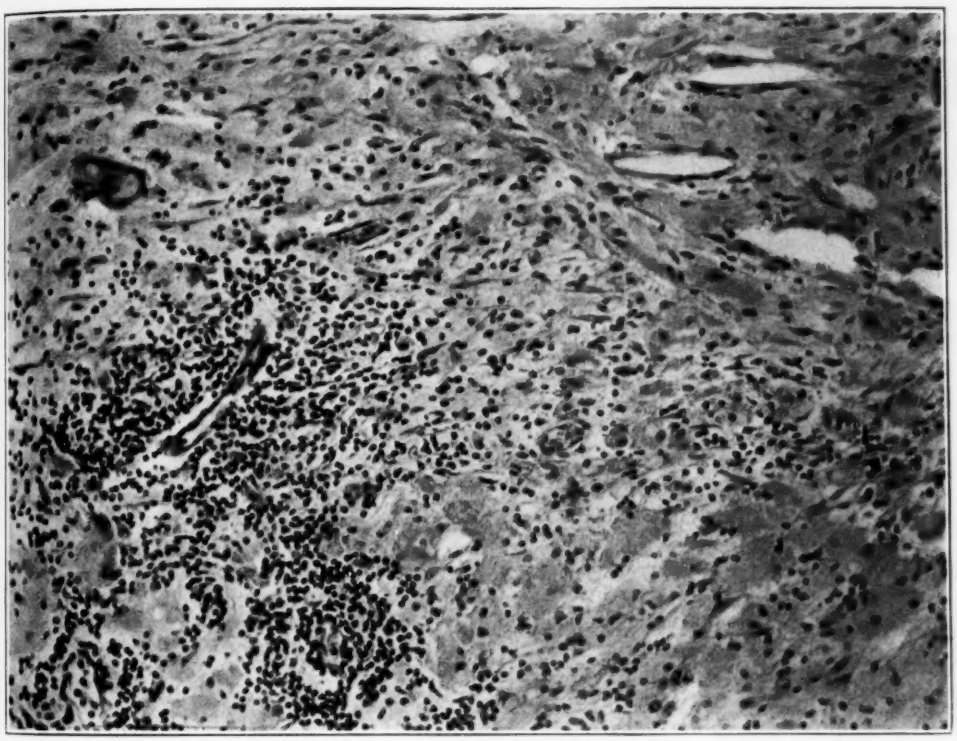

Fig. 3.—Section from a solid nodule of tissue from a dermoid cyst, showing connective tissue, epithelial cells without particular arrangement, fat cells, capillaries and clefts filled with cholesterol, in an arrangement commonly seen in dermoid ("teratoid") tumors. Hematoxylin and eosin; × 190.

weeks later, has since married and has had no recurrence of any of her former symptoms (fig. 3).

CASE 4.—J. V., a boy aged 2 years, was brought to the hospital because of persistent vomiting for eight months, staggering gait for two months and extreme fretfulness and loss of appetite. Prior to the onset of the vomiting he had begun to walk normally, seemed alert and intelligent but made no attempts at talking. The vomiting began with an attack of influenza and continued unabated to the

date of admission to the hospital. For two months he had lurched from side to side when walking, and if left standing alone would fall either forward or backward. For one week he had been completely unable to stand. For six months the mother had noted a rapid increase in the size of his head and had noticed also that he held the head tilted to the left. For three weeks there had been persistent internal rotation of the left eye, and it became increasingly obvious that the child could not see well. Furthermore, he stopped saying the few words that he had managed to learn and emitted only a peculiar grunting sound.

His birth had been normal; he was well developed and had never received an injury to his head.

When examined he was found to be extremely irritable and easily frightened. There was prominent frontal, parietal and occipital bulging of the head, which measured 55 cm. in its greatest circumference. He refused to lift his head from the pillow. There was a positive Macewen note when the skull was percussed. The disks were pale and greatly swollen; the retinal veins were engorged and tortuous, and many fine retinal hemorrhages were seen. The right pupil was larger than the left; both were dilated and reacted only sluggishly to light. There was no nystagmus. The left eye was not moved laterally but rested most of the time in a position of internal strabismus. There was no facial weakness and no apparent loss of sensation in the trigeminal area on either side. He used both hands and legs equally well. The right knee jerk was greater than the left; ankle clonus and a strong Babinski sign were elicited on the right side. There was no apparent loss of sensation at any point on the body. Forward flexion of the head caused him to cry out with pain.

Roentgenograms of the skull showed prominent convolutional markings and separation of the suture lines.

A diagnosis of tumor of the posterior fossa, most probably medulloblastoma, was made. However, on Feb. 24, 1941, at the time of the operation, a change in this diagnosis was made, after the head had been shaved and the scalp was being prepared. Immediately over the site of the external protuberance there was a small scar in the skin, and a low, soft, subcutaneous nodule could be felt. With slight pressure a droplet of sebaceous material escaped from the scar, and this fact, together with the information obtained in the history that from this area a "sebaceous cyst" had been removed when the child was 4 months old, led to the diagnosis of dermoid cyst. A midline suboccipital craniectomy was done, and immediately a firm, yellow, spherical mass, the size of a small English walnut, was observed lying exactly in the midline, just caudal to the external occipital protuberance. It appeared to be contained within the layers of the dura mater, with an upward extension by a cordlike process through the bone to the small area of scar on the scalp. The mass was opened with the electrocautery, and there was an immediate extrusion of thick, cheesy, white and green material, together with masses of hair and particles which looked like flakes of cartilage. The entire wall of the cavity was cleansed free of this material. It was then apparent that the mass did not extend to the subarachnoid spaces but was enclosed on all sides by true dura mater. The walls of the cavity were coagulated; the remaining dead space was eliminated by fine silk sutures, and the wound was closed without drainage. The histologic diagnosis was dermoid (teratoid) tumor. Except for the age of the patient, this history corresponds closely to that in the case reported by Quade and Craig,[11] especially as to the location and gross appearance of the tumor.

11. Quade, R. W., and Craig, W. M.: Proc. Staff Meet., Mayo Clin. **14**:459, 1939.

The child made a good recovery from the operation; his appetite and disposition rapidly improved, and he was soon able to walk steadily when led by one hand. Nine months after operation there was still some residual weakness in the left lateral rectus muscle.

CASE 5.—S. K., a housewife aged 59, was well until eight years prior to her admission to the hospital. At that time she began to notice unsteadiness in gait, so that she was soon forced to walk with a cane. Eventually she could walk only with assistance. At the same time a loud ringing developed in the left ear, which persisted for a year, at the end of which period she became totally deaf in that ear. For one year she had had increasing clumsiness in the use of the left

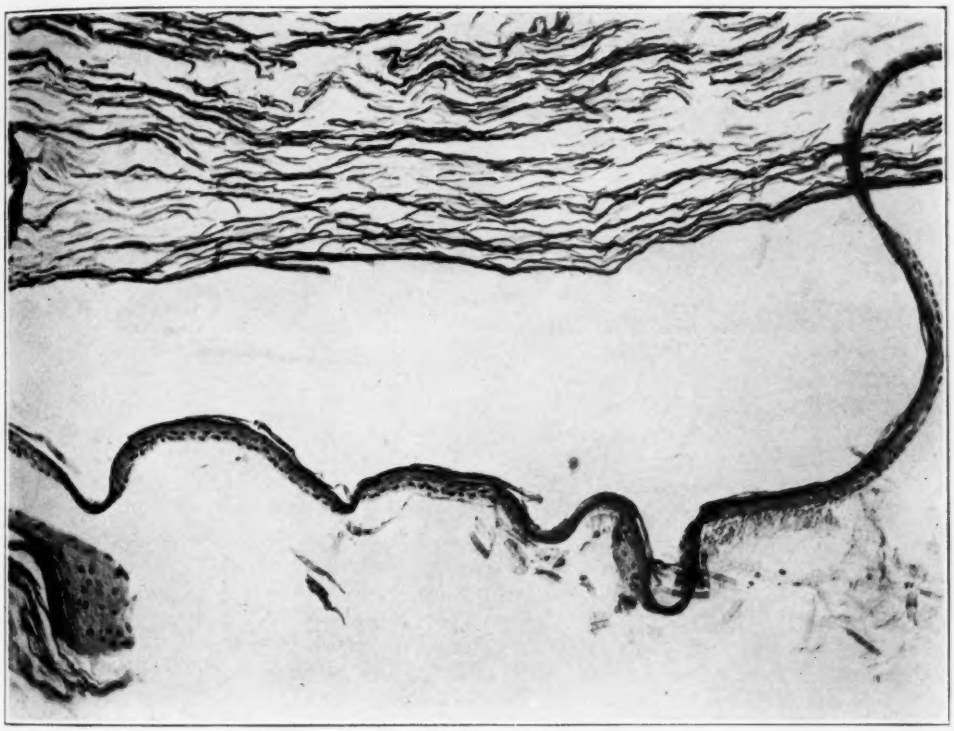

Fig. 4.—Epidermoid tumor. Note the simple arrangement of cells comprising the wall of the tumor. The process of superficial desquamation is well illustrated. The wiry, striated-appearing mass is composed of fixed cholesterol and epithelial debris. Hematoxylin and eosin; × 145.

arm and hand, and for the same period she had had pronounced double vision on looking to either side, so that most of the time the left eye was held shut. For eight months she had suffered episodes of projectile vomiting, not related to meals, and her weight had decreased 40 pounds (18.1 Kg.). She had occasional headaches of a generalized nature. Of recent months there had been a tingling sensation in the left maxillary area. There was no history of trauma to the head at any time, and her past medical and surgical history was without significant incidents.

When the patient was first seen in the hospital she vomited readily on sudden change in position of the head, always fell to the left when she attempted to stand or walk and held her head with the occiput directed toward her left. The pupillary reflexes were normal, and the fields of vision were intact. The left palpebral fissure was slightly wider and the left nasolabial fold appeared shallower than the right. There was no papilledema. On looking to either side, she had

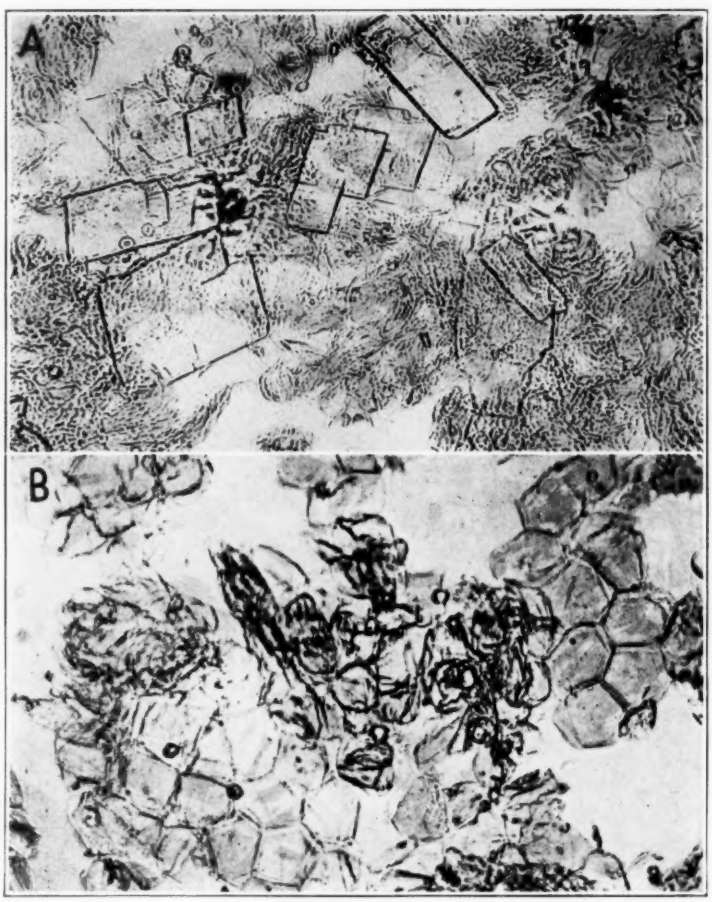

Fig. 5.—Wet smear in glycerin of material from an epidermoid. *A*, a small cluster of cholesterol crystals, together with other amorphous material. Note the typical notched corner on the crystals. × 225.

B, free desquamated epithelial cells, frequently seen in such mosaic-like formation, all of their five or six sides touching other cells to form sheets, such as are shown here. × 300.

coarse nystagmus, with the quick component to the side of fixation. On her looking upward, the left eye did not rotate as far as the right, and nystagmus was produced, with the movement upward and to the right. The left corneal

reflex was diminished, and though she complained of various peculiar paresthesias in the left side of the face, there was no loss of sensation to pain and light touch in that area. The caloric test failed to elicit any response whatever in the left ear. The palatal and pharyngeal muscles were unimpaired, and she swallowed without difficulty. There were pronounced dysmetria and ataxia of both the left arm and the left leg. She appeared to have practically no control over the left arm when purposeful movements were attempted, though there was no loss of muscle power. The left biceps reflex was greater than the right, but otherwise there were no variations in either the deep or the superficial reflexes, and no pathologic reflexes were present.

Roentgenograms of the skull showed no changes from the normal.

On May 26, 1941, a suboccipital craniectomy was performed, with the expectation of finding an acoustic neurinoma on the left side. The bone on the left was unusually thin for an adult, and the left cerebellar hemisphere was plainly lying higher in the operative opening than was the right. The cisterna magna was completely collapsed. The right lateral ventricle was tapped, and this reduced the intracranial pressure sufficiently to allow good retraction of the left hemisphere. Immediately there was exposed a shining, white, finely nodular tumor, the size and shape of a small hen's egg, which lay on and stretched over the surface of the seventh and eighth nerves and extended down to the eleventh nerve. The brain stem was plainly displaced to the right. The tumor appeared to have a thin, onion-skin-like capsule and was completely avascular. When the capsule was opened, the contents were easily and completely removed with a large dull curet, leaving the capsule collapsed like a thin cellophane bag. Then, with gentle traction and separation of the capsule from the surrounding structures with wet cotton pledgets, the entire capsule was removed, the procedure leaving intact the badly thinned-out eighth nerve and the somewhat attenuated seventh nerve. No bleeding followed the removal of the capsule from the side of the brain stem.

The patient made an excellent recovery, left the hospital on the sixteenth postoperative day and forty-five days after her operation was walking alone, though with residual ataxia. She had gained weight, and the diplopia had improved, though there was still some impairment in function of the left abducens nerve. The mild weakness of the left side of the face, present before operation, was somewhat increased afterward, but this, too, showed improvement one month after operation.

Particles of the tumor had a glistening, white, pearly appearance, felt oily between the finger tips and, when floated in water, produced fine oil droplets. Wet smears revealed large masses of cholesterol crystals and much other amorphous material, and stained sections showed the capsule to be made up of one or two layers of squamous or low cuboidal epithelium arranged in simple pattern. The tumor contained no other type of material of cytologic form. The diagnosis was, therefore, epidermoid tumor (figs. 4 and 5).

SUMMARY

A restatement of the definitions of epidermoid and dermoid is necessary for the proper use of these terms:

1. An epidermoid tumor is a benign neoplasm, arising from an embryonic inclusion, or nest of cells. The tumor consists of epidermal cells in various stages of disintegration, together with variable proportions of crystalline cholesterol: This tumor, containing cellular components

only from the epidermis, should not be confused with cholesteatoma, which is a product of chronic inflammation.

2. A dermoid tumor is a benign neoplasm, arising from an embryonic inclusion or nest of cells, the contents of which may represent part or all of the derivatives of the ectoderm.

3. A teratoid tumor contains representatives from the ectoderm and either one of the other two germinal layers. This tumor bridges the gap between the true dermoid and the true teratoma, which contains components of all three germinal layers.

In most large series of verified tumors epidermoids are four times as common as dermoids, but in our own group of over 700 verified intracranial tumors this proportion is reversed.

Epidermoid and dermoid tumors may become manifest at any age, and they do not show any particular relationship to sex, trauma or other incidents in the medical history.

The dermoid occurs at many different intracranial sites, but is frequently attached to the dura mater, is commonly seen in the midline and most often lies below the tentorium cerebelli. The epidermoid is practically always located in the cerebellopontile angle.

Frequently roentgenograms reveal local erosion of bone in the skull, with an area of sclerotic bone immediately surrounding the eroded area, and within the eroded space flecks of calcium may be visible. Such lesions should not be regarded as infallible evidence of the presence of an intracranial epidermoid or dermoid tumor, since other intracranial tumors may produce the same roentgenologic changes.

These tumors may be operated on successfully. In all 5 of our cases the patient has completely recovered from the operation. Two patients who were not immediately relieved of all their neurologic symptoms were greatly improved immediately after operation and are still improving.

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SIBLING DEATHS IN THE ANAMNESES OF SCHIZOPHRENIC PATIENTS

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In the course of an intensive study of several schizophrenic patients the incidental observation was made that the anamnesis contained one or more sibling deaths. The experience of such deaths appeared to have a clear dynamic relationship to the psychotic mechanisms and symptoms of these particular patients. It thus seemed desirable to investigate the frequency of such frustrating situations and, even at the risk of obscuring the important individual dynamics, to approach the problem at first on a purely statistical plane. By comparing the frequency of sibling deaths in the early life history of schizophrenic patients with their occurrence in the early experience of other psychotic patients and in that of a group of normal persons the empiric fact could be evaluated. The elucidation of the results, if positive, was conceived to follow as a more or less independent qualitative study.

METHOD OF INVESTIGATION

The present initial study was limited to males to make possible the accumulation of a homogeneous group of cases sufficiently large for statistical analysis. In examining the case records and questionnaires from which the data of this study were gathered attention was centered on the occurrence of sibling deaths. Since such deaths were regarded as of possible significance in the psychosis only if they occurred during the patient's lifetime and previous to the onset of his illness, only sibling deaths which happened after the patient's birth and before the onset of the psychosis were included. Since, furthermore, the onset of the schizophrenic psychosis is often insidious and difficult to determine but is generally held to lie somewhere in adolescence, the psychosis was arbitrarily assumed for all cases in the study to have appeared by the end of the eighteenth year. Concretely, therefore, all sibling deaths which took place after the birth of the patient and before the beginning of his nineteenth year of life were counted as of possible significance. Such conditions would obviously have much less, if any, value for the control groups, but for control purposes they were necessarily invoked there too.

The data on the psychotic patients were obtained from the examination of 640 case records at the Worcester State Hospital. These records were selected

From the Research Service of the Worcester State Hospital.
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from three diagnostic groups: (1) patients with schizophrenia, in which the chief interest of the study lay; (2) patients with manic-depressive psychosis, and (3) patients with dementia paralytica. The last two served as control psychotic groups.

Rigorous criteria were established for the acceptance of case records. All records in which definite information about sibling deaths was given were included. Statements such as "two brothers died in infancy" were not acceptable since they left doubt as to whether the patient was yet born. While, in keeping with the criteria, no case record was included unless the information on sibling deaths was unambiguous, this provision was not extended to all sibling deaths mentioned. For most purposes in the present study the percentage of subjects with a sibling death rather than the characteristics of the dead siblings was of chief interest. Any case in which unequivocal data on some one dead sibling were given could therefore be included. When the death of a sibling was not mentioned, the record was retained only if the informant was mother, father, brother, sister or some other person who, to judge from the general quality and detail of the childhood information, would apparently have known of such a death had it occurred.

By these criteria only 356, or 56 per cent, of the 640 case records examined were found adequate. Table 1 shows the distribution of the records for each

TABLE 1.—*Percentage of Adequate Case Records for Each Psychotic Group*

Diagnostic Group	Number of Case Histories Examined	Number of Case Histories Accepted	Percentage Accepted
Schizophrenia	195	124	64
Manic-depressive psychosis	188	102	54
Dementia paralytica	257	130	51
Total	640	356	56

diagnostic group. While the differences in the percentages of adequate records are not statistically significant, the fact that the greatest number was obtained for the group with schizophrenia and the smallest for the group with dementia paralytica is possibly explained by the modal age of onset of the psychosis. The earlier the onset the greater the likelihood that a member of the immediate family will be still alive to provide the early history. Moreover, the schizophrenic patients in the study consisted largely of a special research group on whom data had been obtained rather carefully.

From each of the 356 adequate case records the following items of information were taken: diagnosis, age, age at onset of psychosis, total number of siblings, patient's ordinal position in the family, occurrence of sibling deaths, age of patient at time of such deaths, relative difference in age between the patient and the dead sibling, death of mother or father and age of patient at time of such death. For most of the patients additional data were gathered concerning religion, education, native country and parents' native country. The information beyond that directly concerned with death of siblings was included to serve as a context for the final analysis of the results.

Normal control data were gathered by a questionnaire covering the chief points listed in the preceding paragraph. It was sent to 250 persons comprising a group of attendants at the Worcester State Hospital, applicants at the United States Employment Office in Worcester, Mass., members of the Worcester Y. M. C. A. and classes at Clark University, American International College and

Tufts College.[1] Socioeconomically, the hospital attendants and employment office applicants were regarded as approximately matched with the psychotic patients, since they represented either a low income group ($10 per week plus maintenance) or the unemployed. To test this matter with the other groups sampled, the Y. M. C. A. members and two of the college groups (Clark University and American International College) were asked to indicate their average monthly rentals. The median of these amounts was $37, which is slightly higher than that found by Faris and Dunham [2] (page 243) for schizophrenic patients as a group but lower than the figures for patients with dementia paralytica and manic-depressive psychosis. Since it is impossible to determine how closely the patients at the Worcester State Hospital resembled socioeconomically those investigated by Faris and Dunham in Chicago, this comparison is at most indicative of only a rough matching between the normal and the psychotic subjects in the present study. For this reason special care must be exercised in the evaluation of such differences between the groups as are revealed by the data.

TABLE 2.—*Percentage of Subjects with a Sibling Death During the Subject's Childhood or Adolescence*

Group	Number of Subjects	Number with Sibling Deaths	Percentage	Standard Deviation of Percentage
Schizophrenia	124	49	39.5	±0.044
Manic-depressive psychosis	102	26	25.5	±0.042
Dementia paralytica	130	30	23.1	±0.037
Normal subjects	250	41	16.4	±0.022
Critical ratios of percentage differences:				
Schizophrenia : manic-depressive psychosis				2.30
Schizophrenia : dementia paralytica				2.88
Schizophrenia : normal subjects				4.72
Manic-depressive psychosis : dementia paralytica				0.42
Manic-depressive psychosis : normal subjects				1.90
Dementia paralytica : normal subjects				1.49

As a final control—in a sense supplementary to the sample of normal subjects just described—the life expectancy tables of the United States Bureau of the Census were consulted. An effort was made to discover from them the extent to which the incidence of sibling deaths for the present subjects agreed with the general expectancy of such deaths for the whole population. This control was designed to bring out any difference there might be between the schizophrenic and the other groups when the sibling deaths actually found and those theoretically expected were compared.

RESULTS OF STUDY

From the data yielded by the case records and the questionnaires the percentage of subjects with sibling deaths as previously delimited was ascertained. The results are presented in table 2. The schizophrenic patients clearly had more brothers and sisters who died than did any of the other groups, the percentage being 39.5. On further analysis of

1. These institutions cooperated generously in this study.

2. Faris, R. E. L., and Dunham, H. W.: Mental Disorders in Urban Areas, Chicago, University of Chicago Press, 1939.

the data, the various subtypes did not appear to be significantly differentiated in this connection, though the groups involved were too small for statistical reliability. The value for the schizophrenic patients as a whole was 14 per cent higher than that for the group with manic-depressive psychosis. The group with dementia paralytica came next, with 23.1 per cent. The normal group was lowest, with 16.4 per cent. The critical ratios of the differences between the percentages show that the schizophrenic group varied in a statistically reliable way from both the normal group and the groups with dementia paralytica.[3] The critical ratio of 2.30 between the schizophrenic group and the group with manic-depressive psychosis was more problematic. However, even here there were 98.9 chances out of 100 in favor of a real difference. There was no other critical ratio over 2.00.

As previously noted, the normal group should be scrutinized more carefully. There is a possibility that it was too heavily weighted with college students to be representative despite the rough socioeconomic matching already mentioned. In order to test this possibility, all college students were excluded from the group. Hospital attendants, unemployed men and a few Y. M. C. A. members—a total number of only 77—were now left. Of these, 15, or 19.5 per cent, showed sibling deaths, as compared with 16.4 per cent for the whole normal group. The critical ratios were the same as before. The schizophrenic patients had significantly more sibling deaths than the normal subjects (critical ratio 3.17), but there were no significant differences between the normal subjects and the other two psychotic groups. The normal sample was not, then, particularly distorted, if at all, by the inclusion of the college students in question.

Thus far the number of patients in whose family history a sibling death was encountered has been considered. It may now be noted further that any particular patient, or normal subject, might have more than 1 such death in his anamnesis. It is of interest to inquire as to the gross number of sibling deaths found among schizophrenic patients as compared with the number for other groups. The figures are given in table 3. The data show that for the 124 schizophrenic patients there were 67 sibling deaths, or 54 per hundred. For the 102 patients with manic-depressive psychosis the corresponding figures were 37 and 36 respectively; for the 130 patients with dementia paralytica, 39 and 30, and for the 250 normal subjects, 46 and 18. On this basis the schizophrenic patients were even more sharply distinguished from the other groups of subjects than when the percentage of patients with a sibling

3. In this paper a critical ratio of 2.78—McCall's criterion (How to Measure in Education, New York, The Macmillan Company, 1922, page 404)—is taken as indicating practical certainty. Such a ratio means that there are 9,973 chances out of 10,000 that there is a real difference between the groups.

death in the anamnesis was considered. The critical ratios for the differences per hundred between the schizophrenic and the other groups were all high. The only questionable ratio, again, concerned that for the schizophrenic patients and the patients with manic-depressive psychosis—a result which is substantiated by the significant difference further found between patients with manic-depressive psychosis and normal subjects. This fact will be considered in the interpretation of the results.

If a sibling death is interpreted as having a given effect on survivors, the present results may point to a reenforcing factor, since they show not only that more schizophrenic patients have a sibling death in their anamnesis but that they have a considerably higher per hundred rate of such deaths than do other groups. In the sequel, however, it will for the most part be the percentage of patients with sibling deaths rather than

TABLE 3.—*Total Number of Sibling Deaths*

Group	Number of Subjects	Number of Sibling Deaths	Number per Hundred Subjects	Standard Deviation
Schizophrenia	124	67	54	±0.045
Manic-depressive psychosis	102	37	36	±0.048
Dementia paralytica	130	39	30	±0.040
Normal subjects	250	46	18	±0.025
Critical ratios of differences per hundred:				
Schizophrenia : manic-depressive psychosis				2.73
Schizophrenia : dementia paralytica				4.00
Schizophrenia : normal subjects				6.93
Manic-depressive psychosis : dementia paralytica				0.97
Manic-depressive psychosis : normal subjects				3.33
Dementia paralytica : normal subjects				2.56

the number of sibling deaths per hundred patients in a group which will be alluded to, since it is the extent of this type of event rather than its concentration which must in the first instance be given attention.

The fact that schizophrenic patients had a sibling death in their anamnesis significantly more often than did normal subjects or patients with dementia paralytica, and considerably more often than did patients with manic-depressive psychosis, has now been presented. It becomes necessary to inquire as to possible extraneous variables which may account for this difference.[4] One possible factor of this sort is average

4. In view of the decreasing mortality rates for recent years, it should perhaps be considered in passing whether any error from this source is present in the results. The mean age expressed in years for each of the groups of subjects was as follows: schizophrenic patients, 28; patients with manic depressive psychosis, 46; patients with dementia paralytica, 45, and normal subjects, 26. From these figures it is easy to deduce that if an experimental error due to change in mortality rates is present, it must be reflected in the data for the subjects with manic-depressive psychosis and dementia paralytica, who were about 20 years

(Footnote continued on next page)

family size, for it is obvious that persons from larger families would have more chances of a sibling death. Table 4 presents the mean family sizes of the various groups of subjects for all cases in which this information was obtainable and shows that the schizophrenic patients did in fact come from the largest families. The mean number of siblings was 5.7. The average number for patients with dementia paralytica was 5.3, and for the patients with manic-depressive psychosis and the normal subjects the means were 4.7 and 3.7 respectively. The critical ratios between the various means indicate that the normal group had significantly fewer siblings per subject than any of the psychotic groups. This result suggests that though the normal group might be close to the psychotic groups in economic status, the college subgroup possibly represented a selection on the basis of small families. There was no

TABLE 4.—*Mean Number of Siblings in the Families of the Various Groups of Subjects*

Group	Mean Number of Siblings	Standard Deviation of Mean
Schizophrenia	5.7	±0.0277
Manic-depressive psychosis	4.7	±0.295
Dementia paralytica	5.3	±0.250
Normal subjects	3.7	±0.135
Critical ratios of differences:		
Schizophrenia : manic-depressive psychosis		2.44
Schizophrenia : dementia paralytica		1.05
Schizophrenia : normal subjects		6.45
Manic-depressive psychosis : normal subjects		3.03
Dementia paralytica : manic-depressive psychosis		1.54
Dementia paralytica : normal subjects		5.52

significant difference in this respect between schizophrenic patients and patients with dementia paralytica or between the latter and the patients with manic-depressive psychosis. There is, however, a strong indication (critical ratio 2.44) that the patients with manic-depressive psychosis had fewer brothers and sisters than the schizophrenic patients.

It having thus been found that schizophrenic patients do come from larger families, it becomes necessary to test whether the incidence of sibling deaths is greater among schizophrenic patients when the size of the family is controlled.

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older than the others, and would make for a death incidence somewhat too high for comparative purposes. Since, however, the death incidences for these control psychotic groups were definitely lower than the mortality rate for the experimental group of schizophrenic subjects—and in this lies the point of the comparison—any such possibility of error must be construed as having attenuated the reported differences. The difference between the schizophrenic and the normal group, on the other hand, is so small as to be negligible.

Table 5 gives the percentage of sibling deaths for each family size in every group. (In a few instances the size of the family could not be ascertained, and these cases had therefore to be omitted.) In general the schizophrenic patients appeared to have the highest percentages of sibling deaths regardless of family size. There were only two points at which the figures for the schizophrenic group fell much lower than the percentages for the other groups. One was at the 2 sibling level, where

TABLE 5.—*Percentage of Sibling Deaths According to Size of Family*

	Schizophrenia		Manic-depressive Psychosis		Dementia Paralytica		Normal Subjects	
Family Size	Number of Patients	Percentage with Sibling Deaths	Number of Patients	Percentage with Sibling Deaths	Number of Patients	Percentage with Sibling Deaths	Number of Subjects	Percentage with Sibling Deaths
1	5	..	10	..	9	..	33	..
2	8	0	5	0	11	0	51	16
3	19	16	16	6	12	0	49	16
4	22	41	10	10	18	6	38	13
5	17	59	10	30	16	31	29	10
6	14	14	16	21	8	38	23	30
7	7	43	12	33	14	29	13	38
8	8	56	2	50	14	46	7	29
9	9	67	8	50	6	67	1	0
10	4	75	2	50	3	67	3	67
11	2	100	0	..	1	0	0	..
12	1	100	2	100	4	75	0	..
13	4	75	2	100	1	100	1	0
14	0	..	1	100	0	..	0	..
15	1	0	0	..	0	..	0	..
16	1	100	0	..	0	..	0	..

TABLE 6.—*Percentage of Subjects with Sibling Deaths in Families of Two to Six Children*

Group	Number of Subjects	Number with Sibling Deaths	Percentage with Sibling Deaths
Schizophrenia	80	24	30
Manic-depressive psychosis	57	7	12
Dementia paralytica	65	9	14
Normal subjects	190	31	16

none of the psychotic groups showed a sibling death. The normal subjects here showed 16 per cent. The other point was at the 6 sibling level, where the percentage of sibling deaths for schizophrenic patients fell to 14. Because of the large percentages immediately above and below this level, the last figure may perhaps be regarded as a chance fluctuation.

Since the number of cases for each family size is small, it is desirable to reduce the subdivisions by grouping. Families of 6 children or less may be considered first. Families with only 1 child naturally are excluded here. The results are presented in table 6, from which it appears that the schizophrenic group had 30 per cent sibling deaths while the group

with manic-depressive psychosis and the group with dementia paralytica showed 12 and 14 per cent respectively. The normal group had 16 per cent.

Families of 2, 3 and 4 children may next be examined. These family sizes are smaller than the average in any of the psychotic groups. The results are given in table 7. The schizophrenic patients, again, had the largest percentage of sibling deaths, 24, as compared with the group with manic-depressive psychosis, with 7, the group with dementia paralytica, with 2, and the normal group, with 15.

Another method for controlling the size of family and patient's position in the family was suggested by Dr. Forrest E. Linder,[5] of the United States Bureau of the Census. This procedure utilizes a publication of the Bureau of the Census [6] for determining the probability that at least 1 sibling will die in the family of any given subject after that subject's birth but before he is 19 years old. The method consists essentially in calculating the probability of the death of each sibling

TABLE 7.—*Percentage of Subjects with Sibling Deaths in Families of Two to Four Children*

Group	Number of Subjects	Number with Sibling Deaths	Percentage
Schizophrenia	49	11	24
Manic-depressive psychosis	31	2	7
Dementia paralytica	41	1	2
Normal subjects	138	21	15

in a hypothetic family of the same size and sibling configuration as the subject's family and then determining the total probability of at least 1 such death in the family.[6] Linder's method was slightly modified in its application here to make it practicable for the data on psychotic patients, for it was not always possible to ascertain the exact ages of their individual siblings. The spacing between children was accordingly assumed to be two years in all cases and in all groups. Moreover, only the life tables for males were used.[7] To eliminate the effects of extremely large families and of only children, the subjects coming from families of from 2 to 9 siblings were alone considered. The results obtained with this life table method were compared with those given by the actual examination of the case records to determine how closely the samples employed in the present study were representative of the

5. Dr. Linder gave helpful suggestions in the present connection and made a critical reading of the manuscript. For details of the method see the appendix.

6. Vital Statistics—Special Reports, 1930, United States Department of Commerce, Bureau of the Census, 1936, vol. 1, no. 20, pp. 389-399.

7. The validity of the two foregoing modifications is considered in the appendix.

total population of the United States in mortality rates. Any isolated deviation might indicate that the sample in question represented a unique frequency of sibling deaths.

Table 8 presents the figures empirically obtained as compared with those to be expected from the life tables. Of the 211 normal persons falling within the prescribed range of family sizes, 37.1, or 18 per cent, would be expected to have had sibling deaths. In actuality they had 38, or 18 per cent. The agreement is exact. The agreement for the figures for the group with dementia paralytica and that with manic-depressive psychosis is nearly as close. For the 99 in the former group, 28.7, or 29 per cent, would be expected, whereas 23, or 23 per cent were found empirically. For the 79 in the latter group, 20.3, or 26 per cent, would be expected, while 18, or 23 per cent, were actually found. The differences between the theoretic expectations and the empiric findings for these two groups are therefore small, — 6 and — 3 per cent respectively,

TABLE 8.—*Number of Subjects Expected and Found to Have Sibling Deaths*

Group	Total Number of Subjects	Number Expected	Percentage Expected	Number Found	Percentage Found	Percentage Difference
Schizophrenia	104	24.8	24	38	37	+13
Manic-depressive psychosis	79	20.3	26	18	23	— 3
Dementia paralytica	99	28.7	29	23	23	— 6
Normal subjects	211	37.1	18	38	18	0

and indicate that slightly fewer deaths were found in the case records than would be expected from the life tables. Of the 104 schizophrenic patients, however, 24.8, or 24 per cent, would be expected to have had sibling deaths associated with them, whereas 38, or 37 per cent, actually did have. Here the difference is + 13 per cent, a result showing that this group of subjects had considerably more sibling deaths than would be expected from the life tables and that the deviation thus probably represents a unique rate. This finding is the more striking because the other three groups, by their close agreement between expected and actual figures, tend to support the validity of this method for controlling family size and the patient's position in the family.

It may be concluded from the two foregoing methods of controlling family size—one based on matching for number of siblings and the other utilizing life table expectancies—that schizophrenic patients appear to have more sibling deaths in their life histories up to the age of 19 years than do the other groups of subjects, regardless of the number of siblings in the family. It is not possible to account for the discovered difference in frequencies of sibling deaths on the basis of family size.

Another variable which must be considered in evaluating the results on sibling deaths is the socioeconomic status of the various groups. Since all of the patients in the study were drawn from one state hospital, it was considered that they were representative of approximately the same level in this regard. It will be recalled that an effort was also made to evaluate the extent to which the normal subjects resembled the patients in socioeconomic status by reference to monthly rentals, and it appeared that a rough similarity existed. However, the degree to which the various groups of subjects were matched on this point cannot be regarded as completely adequate, and further investigation should direct itself toward a better control of this factor. In the meantime it must be borne in mind that by the psychodynamic interpretation shortly to be considered the lower socioeconomic levels might through their higher death rate more readily provide one of the very conditions necessary for the development of schizophrenia. Whether such deaths are truly determinative can, however, be ascertained only by a study of families of schizophrenic patients and control families in the higher socioeconomic levels, in which a significantly greater frequency of deaths for the schizophrenic than for the other groups could not possibly be attributed to economic conditions and would point unambiguously to some selective aspect of schizophrenia itself.[8]

Having considered the possible effect of extraneous variables on the observation that schizophrenic patients have a significantly high incidence of sibling deaths in their life histories, such qualifying information about these deaths as is available may now be presented.[8a] The first point of this kind concerns the sex of the dead siblings. The data on the 56 dead siblings of schizophrenic patients for whom the required sex designation could be obtained showed that 30, or 54 per cent, were

8. Though the results of the present study converge at this point with those of Faris and Dunham,[2] it is unfortunate that their data are not sufficiently comparable to permit of any significant conclusions. While emphasizing that schizophrenia tends to increase as one approaches the more disorganized ecologic areas of their investigation, they fail to bring this fact into relation with an almost identically parallel trend in the death rate, as shown in table 76 in their book. Possibly their concept of "isolation" is intended to cover the latter relationship by implication, but from the standpoint of the present study there arises the question whether this relation did not deserve a much more prominent place in their analysis. For it is conceivable that this relationship between death rate and ecologic area specifies an important constituent of "isolation" in the same manner as the presence of the Anopheles mosquito is a more specific condition for the incidence of malaria than is a swampy, hot habitat.

8a. Such qualifications regarding the deaths of the normal subjects are not given, since the interest of the study was obviously limited to the deaths in the schizophrenic group. Comparison with the other subjects was necessary for control purposes only where the statistical significance of the frequency of deaths in the schizophrenic group was in question.

males and 26, or 46 per cent, were females. In statistical terms, therefore, the sex of the dead siblings cannot be regarded as having any significance.

Another matter of interest is the patient's position in the family. Though it has been shown by Malzberg [9] that position in the family does not in general correlate with incidence of psychosis, it seemed worth while to inquire whether some such relationship might not exist in the present, more specialized situation. Concretely, the attempt was made to ascertain whether the schizophrenic patients with sibling deaths fell more frequently in the upper or the lower half of the family. It was found that 72 per cent belonged in the former and 28 per cent in the latter position.

Further information in the same connection is found in the answer to the question whether the patient was more often older or younger than his dead brother or sister. In this inquiry it was necessary to count all dead siblings (but only those for whom the necessary information could be obtained), since it was impossible to tell which sibling death to select for a given patient. In some instances the same patient had, accordingly, to be included more than once in the calculations, and the results are therefore open to some question. What they show is that of the 61 dead siblings considered, 47, or 77 per cent, were younger while 14, or 23 per cent, were older than the patient. The preceding result is thus corroborated.

A further problem concerns the age of the schizophrenic patient at the time of the sibling death. In view of the generally recognized psychologic vulnerability of the child, it seemed well to inquire as to the proportion of sibling deaths which occurred while the subjects were very young. The number of sibling deaths taking place before the subject's sixth year of life was accordingly determined. Here, again, as with the preceding data, it was necessary to count all dead siblings (but only those for whom the required information could be obtained), so that the figures are not completely consistent with those presented earlier. It was found that of the 61 sibling deaths for the 118 schizophrenic patients, 34, or 56 per cent, occurred before the patient was 6 years old—a six year span—while 27, or 44 per cent, occurred between the patient's sixth and nineteenth year—a thirteen year span. There is thus a clear tendency for these deaths to concentrate in the early childhood years of the patient—a fact which may represent an important qualification of these events from the standpoint of psychologic experience.

The data on sibling deaths having thus been presented, some supplementary observations on the death of parents may now be considered.

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9. Malzberg, B.: Is Birth Order Related to the Incidence of Mental Disease? Am. J. Phys. Anthropol. **24**:91-104, 1938.

The relationship between psychosis and parental death has been previously investigated by Barry [10] and by Barry and Bousfield.[11] Barry's study was of a historical nature, showing that twice as many insane as sane kings had lost their fathers early in life. Barry and Bousfield determined the percentage of a group of 1,500 psychotic persons who had lost either parent by the age of 12 years. They found that 27.6 per cent had experienced such a death, as compared with 20 per cent for normal control data. No differentiation among the psychoses was made in their study.

TABLE 9.—*Paternal, Maternal and Parental Deaths Among Psychotic and Normal Subjects*

Group	Number of Subjects	Number with Death of a Parent	Percentage	Standard Deviation of Percentage
Paternal Deaths				
Schizophrenia	117	25	21	±0.037
Manic-depressive psychosis	95	9	10	±0.030
Dementia paralytica	112	14	12.5	±0.032
Normal subjects	164	19	12	±0.024
Critical ratios of percentage differences:				
Schizophrenia : manic-depressive psychosis				2.29
Schizophrenia : dementia paralytica				1.73
Schizophrenia : normal subjects				2.05
Maternal Deaths				
Schizophrenia	116	8	7	
Manic-depressive psychosis	96	8	8	
Dementia paralytica	121	8	7	
Normal subjects	162	4	3	
Parental Deaths				
Schizophrenia	117	33	28	±0.041
Manic-depressive psychosis	96	17	17.5	±0.039
Dementia paralytica	121	22	18	±0.035
Normal subjects	164	23	14	±0.026
Critical ratios of percentage differences:				
Schizophrenia : manic-depressive psychosis				1.84
Schizophrenia : dementia paralytica				1.82
Schizophrenia : normal subjects				2.86

In the present investigation the number and percentage of paternal, maternal and total parental deaths before the subject's nineteenth year were determined for all groups separately. (In some instances, particularly among the normal subjects, the information could not be obtained, and the totals for the groups thus vary somewhat from those previously given.) The results are shown in table 9. Of the schizophrenic group 21 per cent had lost their fathers, whereas only 10 per cent of the group with manic-depressive psychosis, 12.5 of the group with dementia paralytica and 12 per cent of the normal group had had such a loss. Maternal

10. Barry, H.: Orphanhood as a Factor in Phychoses, J. Abnorm. & Social Psychol. **30**:431-438, 1936.

11. Barry, H., and Bousfield, W. A.: Incidence of Orphanhood Among Fifteen Hundred Psychotic Patients, J. Genet. Psychol. **50**:198-201, 1937.

deaths occurred infrequently—3 to 8 per cent—among the present subjects, and at no point did the groups show any particular differentiation in this respect. When parental deaths as a whole were considered, the schizophrenic groups once more had the highest incidence, 28 per cent, as compared with 17.5 per cent for the group with manic-depressive psychosis, 18 per cent for the group with dementia paralytica and 14 per cent for the normal group. Moreover, the critical ratio of the percentage difference between the schizophrenic and the normal group was now 2.86 and was thus statistically significant. The other critical ratios were all below the level of significance. The present results corroborate those of Barry and Bousfield, but indicate further that it is chiefly in the schizophrenic group that the higher incidence of parental deaths among psychotic patients is apparently found. They also show that it

TABLE 10.—*Incidence of Sibling or Parental Deaths Among Psychotic and Normal Subjects*

Group	Number of Subjects	Number with Deaths	Percentage	Standard Deviation of Percentage
Schizophrenia	118	72	61	±0.045
Manic-depressive psychosis	96	32	33	±0.048
Dementia paralytica	121	50	41	±0.045
Normal subjects	164	46	28	±0.035
Critical ratios of percentage differences:				
Schizophrenia : manic-depressive psychosis				4.24
Schizophrenia : dementia paralytica				3.12
Schizophrenia : normal subjects				5.79
Manic-depressive psychosis : normal subjects				0.85
Dementia paralytica : manic-depressive psychosis				1.21
Dementia paralytica : normal subjects				2.28

is in respect to paternal rather than to maternal deaths that the higher incidence appears.

The results on parental deaths may now be considered in association with those on sibling deaths. According to the combined results, presented in table 10, 61 per cent of the schizophrenic group had either a sibling or a parental death before the age of 19 years.

The corresponding figure for the group with manic-depressive psychosis was 33 per cent, for the group with dementia paralytica 41 per cent and for the normal group 28 per cent. Here for the first time every critical ratio for the difference between the schizophrenic and each of the three control groups is statistically significant—5.79 for the normal group, 4.24 for the group with manic-depressive psychosis and 3.12 for the group with dementia paralytica. None of the other critical ratios reach the level of statistical significance.

It may, then, be concluded that in the life histories of male schizophrenic patients immediate familial deaths before the patient arrives at the nineteenth year are found significantly more often than is true of patients with manic-depressive psychosis or dementia paralytica or of

normal subjects. The schizophrenic subtypes do not appear to be particularly differentiated in this respect. Of the patients studied, 61 per cent showed a sibling death, a parental death or both. Sibling deaths distinguished the schizophrenic patients much more sharply from the control groups than did parental deaths. The sibling deaths, which were found in 39.5 per cent of the anamneses, usually involved persons younger than the patient and occurred more often than not before the patient's sixth year. The dead siblings were as often males as females. Such extraneous factors as family size and family configuration do not appear to account for the sibling death figures, but it should be added that until a larger number of subjects has been studied, particularly female patients, and the factor of socioeconomic status has been more fully controlled, the present results must be regarded as indicating merely a strong presumptive trend.

INTERPRETATION

On the assumption that it is generally true, as has been shown for the patients in the present study, that schizophrenic patients more frequently have sibling deaths in their life histories than do other persons, the question of explanation naturally arises. Three possible avenues of theoretic interpretation appear to be open.

1. The first, and in some senses the simplest, view of the matter is that the families of which schizophrenic persons are members suffer from a general constitutional weakness that manifests itself concomitantly in the occurrence of many sibling deaths and in the schizophrenic disease process. This may be called the somatogenic view. Such an interpretation would accord with certain direct, though fragmentary, evidence and with a more or less generally held opinion that schizophrenia is rooted in a constitutional predisposition. No evidence in addition to that already given can be offered here either in proof or in disproof of this hypothesis. A possible approach to the problem in future study lies in the relationship which some investigators believe to exist between the tuberculous and the schizophrenic diatheses.[12]

2. While the somatogenic view tends to relegate both the sibling deaths and the schizophrenic disease process to a common cause, and thus makes them essentially independent of each other, a second possible interpretation might regard these two facts as interdependent, the sibling death serving as a basis for the schizophrenic process. By placing chief

12. Lewis, N. D. C.: The Constitutional Factors in Dementia Praecox, Nervous and Mental Disease Monograph 35, New York, Nervous and Mental Disease Publishing Company, 1923. Luxenburger, H.: Tuberkulöse als Todesursache in den geschwisterschaften Schizophrener, Manisch-Depressiver und der Durchschnittsbevölkerung, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:313-340, 1927; Ueber weitere Untersuchungen zur Frage der Korrelation von schizophrene Anlage und Widerstandsschwäche gegen die tuberkulöse Infektion, ibid. **122**:74-89, 1929.

stress on the psychologic effects of the sibling death as experienced by the surviving sibling, this view goes to the other extreme from that of the somatogenic and may therefore be called the psychogenic interpretation. In its context are relevant the observations of Freud [13] as to the potentially powerful effects of the father's death and the hypothesis of Zilboorg [14] that the death of close relatives or friends in the early life experience of a person may serve as a basis for later suicidal tendencies. It may be noted that it was such psychologic aspects of the problem that, in the study of several individual patients, first drew attention to the possible significance of sibling deaths in schizophrenia.

The psychogenic interpretation would begin by pointing to the great importance of sibling rivalry. From the psychoanalytic standpoint such rivalry is essentially a struggle to gain or to retain the love of the mother in the earliest years of life. It is thus in certain respects similar to the Oedipus situation, in which the male child is a rival of the father for the mother's love. If, now, with reference to the data of the present study, a male child who is firmly entrenched in the mother's love is thought of as suddenly confronted with a sibling that threatens to displace him, intense hostility may be presumed to develop. Rivalry would not be limited necessarily to sibling displacement, since it might be felt toward an older sibling also, but it would probably be maximal when the rival was a newcomer. In any case the hostility involved may be supposed to extend, where the young child is concerned, even to death wishes. In most instances there would exist along with such hostile trends strong libidinal components from various sources. For example, if the displacing sibling were a female, she might in some respects serve as a surrogate for the mother and atone, as it were, for her rivalry by offering the male sibling some degree of feminine love herself. If the rival sibling were a male, he might serve as a father surrogate and help mediate the solution of the Oedipus problem by the establishment of homosexual bonds. But whatever the source of such libidinal accompaniments of the hostility in sibling rivalry, the outcome would be the same: a highly ambivalent relationship between the siblings. It is on such intense ambivalence that any extreme effect of the sibling death would probably depend in the end.

With such a background—intense hostility to the displacing sibling, complicated in some degree by contravalent libidinal trends—let it now be supposed that the rival sibling dies. The hostile wishes against the rival would even in his lifetime have been accompanied by a counter-

13. Freud, S.: Interpretation of Dreams: Authorized Translation of Third Edition with Introduction by A. A. Brill, London, Allen & Unwin, 1913.

14. Zilboorg, G.: Differential Diagnostic Types of Suicide, Arch. Neurol. & Psychiat. **35**:270-291 (Feb.) 1936.

part of guilt feelings. The latter would be all the more intense if the hostility was directed toward some one who was at the same time loved. Now that the death wishes have, as if by magic, been realized the guilt feelings would become maximally acute.

The significance of sibling rivalry as thus portrayed has been described by numerous writers. Among these may be mentioned Flügel,[15] Klein [16] and Levy.[17] The extent of the hostility engendered by such rivalry has been shown by them to be very great, including death wishes and even acts of fatal violence. Bender and Curran,[18] in a recent report, have given striking examples of children and adolescents who have attempted, successfully or unsuccessfully, to carry out such wishes. More frequently, however, the wishes are not acted on but are important chiefly because they are accompanied by intense feelings of guilt or because events may accidentally bring about their fulfilment in a way that must appear almost magical to the child. In this contingency the guilt feelings which usually form the counterpart of death wishes are, as Feigenbaum [19] has shown, greatly magnified. Schilder and Wechsler [20] concluded from their investigation that the child conceives of death as resulting always from violence and as not necessarily being final. The dead are not gone forever. These observations make it easy to see how a surviving brother or sister could interpret the death of a sibling as having been the result of his or her hostility rather than of natural causes and might, furthermore, look forward to the return of the deceased in a fashion tending to keep the experience of the death alive. Such an expectation would be enhanced by the reparation trends, which as an assuagement of anxiety are generally found to accompany the child's destructive tendencies.

The guilt feelings and anxiety of the surviving sibling might exist, as has already been indicated, in various forms and blends. The particular ambivalent character of the sibling relationship would determine these patterns. If the libidinal components of the attachment had been strong, the guilt would in some measure be increased by feelings of unworthi-

15. Flügel, J. C.: Psychoanalytic Study of the Family, London, Hogarth Press, 1935.

16. Klein, M.: Psycho-Analysis of Children, translated by A. Strachey, New York, W. W. Norton & Company, Inc., 1932.

17. Levy, D.: Studies in Sibling Rivalry, Research Monograph 2, New York, American Orthopsychiatric Association, 1937.

18. Bender, L., and Curran, F. J.: Children and Adolescents Who Kill, J. Crim. Psychopath. **1**:297-322, 1940.

19. Feigenbaum, D.: Paranoia und Magie, Internat. Ztschr. f. Psychoanal. **16**:363-369, 1930.

20. Schilder, P., and Wechsler, D.: The Attitudes of Children Toward Death, J. Genet. Psychol. **45**:406-451, 1934.

ness—for having killed the one from whom love had been received. If any degree of tabooed sexual activity, or even fantasy, entered into the relationship another source of guilt would be tapped. Mourning for the lost object might also combine with the guilt feelings springing from hostility. But the driving power of the reaction would stem from the guilty knowledge that the hostile death wishes had taken effect.

The consequences of such guilt would theoretically be of two kinds, each resembling a different main aspect of the schizophrenic reaction pattern. In the first place, the surviving sibling would be prevented by his isolative guilt and the underlying fear of his externalized aggression (and libido) from making normal social contacts. These inhibitions would affect relationships within and, even more so, outside the family. In the normal development of the person, as has been repeatedly pointed out, conditioning first acquired within the family serves by transfer as a basis for extrafamilial associations. The guilt resulting from the sibling death might thus disrupt the normal transfer of social patterns and serve as a source of the asocial schizophrenic reaction type. When the sibling attachment had involved strong components of love, which would now be linked with the guilt feelings due to the death, libidinal object relationships would likewise be impaired. Hence, both the general asociality of the schizophrenic person and his usual incapacity for libidinal object attachments could in part be traced to the consequence of having experienced a sibling death.

A second consequence of the guilt reaction in the surviving sibling may be regarded as a complement of the first. Whereas the first emphasizes negative behavior—withdrawal from social intercourse—the second points to positive manifestations of a substitutive character. That is, the void created by the death of the sibling, and even more so by the withdrawal from society, begins now to be filled with fantasies that provide substitute satisfactions and tend to stabilize the reactions of the person at an asocial level. Thus would arise autistic, bizarre mannerisms, hallucinations and delusions traceable in greater or less degree to the effects of the sibling death.

The result of these two cooperating tendencies would in the paradigmatic case be the very characteristics of the schizophrenic patient as clinically observed: marked incapacity for social contacts; inadequacy in libidinal object relationships; positive manifestations of a fantastic kind, including hallucinations and delusions, and a strong underlying sense of guilt and anxiety associated with repressed hostility.

That this second, or psychogenic, interpretation is consonant with the results of the present study is clear. It has been shown that the schizophrenic patients came in most instances from the upper half of

their families and that in the majority of cases the dead siblings met their fate before the patient's sixth year of life. These two facts cooperate to emphasize that the schizophrenic patient as a surviving sibling was in the acute rivalry position of having been displaced by a new claimant on the mother's love and that the death of the rival usually occurred in the important formative years of childhood.

If it is recalled that the present study is concerned with male patients only, it will be seen that the interpretation is borne out also by the facts on parental deaths. On the one hand, the father would, like a sibling, represent for such a patient a rival for the mother's love. It would, accordingly, be expected that the incidence of paternal deaths might—as was actually found—be high among patients with schizophrenia. On the other hand, again as actually found, maternal deaths would not play a significant role. However, with the limited data now available, and in advance of a similar study on female schizophrenic patients, the parental deaths cannot be emphasized in the interpretation.

3. According to a third possible view, which combines the preceding two, a constitutional weakness may contribute concomitantly to the sibling deaths and to the schizophrenic disease process. But just as in the case of the deaths the environment would provide certain specific noxae, e. g., microbes, to effect the result, so in the production of schizophrenia traumatic psychologic experiences, such as sibling deaths, would cooperate. A peculiarity of this view is that in relation to schizophrenia the sibling deaths might count twice—once as causally rooted in the common constitutional weakness and again as having traumatic psychologic effects. In other words, the families of schizophrenic patients are weak in constitution and hence suffer many early deaths. On a similar basis, the prospective schizophrenic patient is from birth less active and independent than other persons. He would thus have more than the average sensitivity to siblings and parents and become abnormally attached to them. Intense feelings of hostility and love toward siblings would therefore more readily develop; guilt feelings and anxiety after sibling deaths would be similarly greater. At this point the psychogenic hypothesis presented in the preceding section would apply to complete the interpretation.

This view may be designated as psychosomatic and would, in keeping with present knowledge, seem to be the closest to the truth of the three discussed in this section. It steers a middle course between the two extremes and appears to reconcile them. Even more important is the fact that it sets the stage for further investigation on schizophrenia by a technic which should make it possible to penetrate more deeply than hitherto into the recognizedly specious dichotomy of constitution and experience.

CONCLUSION AND SUMMARY

It must be apparent that from a psychodynamic orientation deaths of other persons besides siblings could serve to produce similar effects. Presumably, parental deaths and, in the present study especially paternal ones, are to be so regarded. The deaths of other close relatives or intimate friends should likewise be considered. Moreover, the type of frustrating experience or deprivation need not necessarily be limited to death. The clinically recognized effect on the growing child of broken homes might, for example, work out similarly. The present study has thus singled out one factor in a psychodynamic class and will, it is hoped, serve to stimulate systematic investigation of some others.

It should also be noted that the disorder resulting from sibling death and cognate frustrating experiences cannot necessarily be limited to schizophrenia. The present data themselves seem to indicate that manic-depressive psychosis is apt to have such factors in the anamnesis, whereas dementia paralytica, for example, does not. In addition, individual cases could have been readily adduced to show how sibling death has apparently been involved in disorders such as epilepsy. Here, too, lies a problem for more extensive research.

For the present, however, conclusions must be limited to schizophrenia, and here it may be said, on the basis of the data from the 356 adequate individual histories studied, that male schizophrenic patients have up to twice as great a chance (39 per cent) of experiencing sibling deaths as do certain control groups (patients with manic-depressive psychosis and dementia paralytica and normal subjects). This observation holds even when extraneous factors, such as size of family, have been statistically controlled. The majority of such deaths occur in siblings younger than the patient and previous to the patient's sixth year of life. When parental deaths are considered together with sibling deaths, it is found that 61 per cent of the schizophrenic patients had one or both in their history. They are in this respect differentiated from all three control groups with statistical significance. Nevertheless, these results must be considered tentative till more subjects, especially females, have been studied.

The interpretation of the results on sibling deaths that seems to accord best with current knowledge is a psychosomatic one, in which a possible constitutional weakness is regarded as having been acted on by disrupting psychologic experience. On the basis of a strong hostility to the sibling that dies—whether founded primarily on rivalry or on ambivalent libidinal trends with intense aggressive components—guilt is acutely intensified in the surviving sibling by the death. A groundwork is thus laid for a disturbance of the normal transfer of social patterns from the familial constellation to the extrafamilial milieu

and for a complementary tendency toward filling the social void with substitutive fantasies. In such a context sibling deaths may be construed as one factor in the production of schizophrenic reaction patterns.

APPENDIX: METHOD FOR DETERMINING THEORETIC PROBABILITY OF SIBLING DEATHS

The method in question is best described in Dr. Forrest E. Linder's own words:

"Suppose, for example, that one is interested in a subject who was born in a given year. It may be assumed that fifteen years after his birth a male sibling was born. When the subject has reached his twenty-fifth year, the sibling will then have reached his tenth year. The question, then, is: 'What is the chance that the younger brother will have died during his possible ten years of life?' To obtain an answer to this question, one looks in column 3 of the life table published by the United States Bureau of the Census,[6] page 392, which gives the expected number who will die out of 100,000 persons starting life. On adding the first ten figures in this column one gets a total of 8,859. That means that out of 100,000 persons starting life, 8,859 will have died. The probability of this sibling's death, therefore, will be 0.08859 ($p_1 = 0.08859$). That is the probability for a family of 2 male children of the specified age distribution (family 1).

"Now consider the case of a larger family (family 2). In this family it may be assumed that the subject in whom one is interested was born on a given date and that his first younger brother was born fifteen years later. Then the probability of this first brother's dying is the same as that of the sibling in the family previously discussed; that is, $p_1 = 0.08859$. It may now be assumed that the second younger brother was born twenty years after the subject. Then, at the time the subject has reached the age of 25 years, the second younger brother will have reached the age of 5 years. What is the probability that the second younger brother will have died? On adding up the first five entries in column 3 one finds the probability of death to be expressed by the formula $p_2 = 0.07931$. The probability that each brother separately might have died has now been found. What is the probability that either one or the other will have died? To find this, one must compute the probability that each brother will not have died, using the formulas: $q_1 = 1 - p_1$, or 0.91141 and $q_2 = 1 - p_2$, or 0.92069. The probability, then, that both brothers will live is equal to $q_1 \times q_2$, which in my example equals 0.8391. Hence the probability that both younger brothers will not live, that is to say, the probability that at least one will have died, is computed as follows: $p_3 = 1 - q_1q_2$, or 0.1609. The way to proceed from here is to observe a random sample of hospital patients

of the diagnostic type in which one is interested without, however, paying any regard to sibling deaths. For each one of these families computations similar to the foregoing ones are made. A tabulation similar to the one which follows can then be constructed:

Family	*Probability of Sibling Death*
Family 1	0.08859
Family 2	0.1609

"The total for the last column (Σp_1) will give the number of deaths to be expected in all the families under observation. The variance will be $\Sigma p_1 (1 - p_1)$. Naturally, if there is more than one family of the same composition, each instance of that family type must be entered in the table as a separate figure. The figure obtained in this way should give an estimate of the expected number of families with one or more deaths if the deaths are occurring according to the life tables of the United States Bureau of the Census. This is not the expected number of deaths. Then, if in the observed sample one actually finds more than the expected number of families, there would be some evidence to substantiate the hypothesis that sibling deaths are a contributing factor in the psychosis.

"In making the foregoing computations, one should note that separate tables are given for white males, white females, Negro males and Negro females. Life tables, of course, vary considerably from state to state and according to economic status and other factors. If these qualifying factors are not provided for in the computations, they of course stand as variables which leave the result in some question."

As noted in the text, the method suggested by Dr. Linder was somewhat modified in its present application. The validity of these variations may be briefly considered. The assumption of a uniform two year spacing between children was necessary because in the data on psychotic patients it was not always possible to ascertain the exact ages of the siblings. Nevertheless, this assumption required testing. Since the normal group contained many small families, the average spacing might well have been greater there. Under these conditions the interval between the birth of a sibling and the nineteenth year of life might be sufficiently increased to change the expected probability of death. If present, this tendency would distort the results for the normal subjects in such a way that more deaths would theoretically be expected than was justifiable. This error would, in turn, decrease the actually appearing difference between expected and actual deaths. To test the assumption, expectancies of sibling deaths for 50 normal subjects were calculated according to actual spacing, as well as for the hypothetic two year spacing. According to the actual spacing of the 50 normal subjects

9.2, or 18 per cent, would be expected to have sibling deaths. With the uniform two year spacing the expectancy was 8.5, or 17 per cent. Thus the assumed and the actual spacing give nearly the same results for this normal group. Any possible distortion would naturally be less for the schizophrenic patients, who came from the larger families. The assumption is therefore considered valid.

The other modification, which consisted in the use of life tables for males alone, appeared justifiable because male and female sibling deaths were evenly balanced in all the groups of the present investigation and because male and female death rates were considered sufficiently similar for the present purposes.

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DISTRIBUTION OF IODINE IN BLOOD SERUM AND IN CEREBROSPINAL FLUID

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Conflicting reports in the literature on the amount and distribution of iodine in the blood and in the cerebrospinal fluid suggested the reinvestigation of these problems with reliable methods. The iodine contents of the serum and spinal fluid were determined for 6 patients who were free from meningeal disorders and had normal spinal fluid proteins. To a second group of 8 similar patients approximately 0.1 Gm. of inorganic iodine in the form of compound solution of iodine U. S. P. was administered daily for three to seven days before the samples of spinal fluid were obtained. Organic iodine in the form of thyroid was given instead of inorganic iodine to an additional patient. Finally, 1 patient with meningovascular syphilis and high spinal fluid proteins was studied. The recently developed permanganate acid ashing method of Riggs and Man[1] avoids the positive errors of previous methods. In addition, in serum by precipitation with zinc sulfate and sodium hydroxide the diffusible inorganic iodine was differentiated from the precipitable (protein-bound), nondiffusible iodine.[2] Furthermore, the determinations were made in duplicate on large aliquots of cerebrospinal fluid obtained in the preparation of patients for pneumoencephalography.

The older literature on cerebrospinal fluid iodine has been reviewed by Katzenelbogen.[3] With the exception of the recent work of Klassen,

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1. Riggs, D. S., and Man, E. B.: A Permanganate Acid Ashing Micromethod for Iodine Determinations: I. Values in Blood of Normal Subjects, J. Biol. Chem. **134**:193, 1940.

2. Man, E. B.; Smirnow, A. E.; Gildea, E. F., and Peters, J. P.: Serum Iodine Fractions in Hyperthyroidism, J. Clin. Investigation **21**:773, 1942.

3. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935.

Bierbaum and Curtis,[4] spinal fiuid iodine has been estimated by older methods which either were not sufficiently sensitive or were subject to positive errors. Consequently, some authors [5] have found considerable amounts, 10 to 20 micrograms per hundred cubic centimeters, while others [6] have obtained the barest traces, even in patients who had been ingesting large amounts of iodine for several months. It is obvious that with this uncertainty as to methods the older data on the relation of serum iodine and cerebrospinal fluid iodine must be interpreted with caution.

METHODS

The spinal fluid used in these studies was collected from each patient when the cerebrospinal system was drained for pneumoencephalographic examination. The puncture was made in the third or fourth lumbar space, and as each 10 cc. of fluid was removed the same amount of air was injected. The first 10 cc. of fluid was taken in a separate tube for cytologic and serologic examination, and the rest was collected in a chemically clean flask for the chemical studies. No iodine was used in the preparation of the patient, and special precautions were taken to see that no iodine was free in the room air.

Iodine was determined on duplicate aliquots of spinal fluid by the permanganate acid ashing method of Riggs and Man.[1] Most aliquots were large, 20 to 80 cc., a factor which increased the accuracy of the determinations. In 4 instances smaller amounts were used, and this fact has been indicated in the table.

Proteins were measured by the Denis-Ayer [7] method for cerebrospinal fluid proteins. The samples of blood were taken shortly before the lumbar puncture. The serum was analyzed for total iodine and protein-bound iodine by methods previously described.[8]

DATA

A variety of patients were studied, as indicated in the table. Six patients presenting various symptoms of early intellectual deterioration or unexplained convulsions, but free from meningitis, tumor of the brain or syphilis, who had not received any iodine except minute amounts in the hospital diet, constituted the

4. Klassen, K. P.; Bierbaum, R. L., and Curtis, G. M.: The Comparative Iodine Content of Blood and Cerebrospinal Fluid, J. Lab. & Clin. Med. **25**:383, 1940.

5. Hirsch, O.: Beitrag zum Basedowproblem, Deutsches Arch. f. klin. Med. **168**:331, 1930. Hahn, A., and Schürmeyer, A.: Ueber den Jodgehalt des Liquor cerebrospinalis, Klin. Wchnschr. **11**:421, 1932. Osborne, E. D.: Iodine in the Cerebrospinal Fluid, J. A. M. A. **76**:1384 (May 21) 1921.

6. Cruchet, R.: Valeur de la perméabilité méningée en neurologie infantile, Compt. rend. Soc. de biol. **2**:591, 1904. Catton, J. H.: Studies of the Spinal Fluid During Iodid Medication by Mouth, J. A. M. A. **67**:1369 (Nov. 4) 1916. Cohen, H.: The Passage of Iodine into the Cerebro-Spinal Fluid, Lancet **1**:127, 1924. Sicard, J. A., and Brecy, M.: Méningite cérébrospinale ambulatoire curable. Cytologie du liquide céphalo-rachidien, Bull. et mém. Soc. méd. d. hôp. de Paris **18**:369, 1901.

7. Ayer, J. B.; Dailey, M. E., and Fremont-Smith, F.: Denis-Ayer Method for the Quantitative Estimation of Protein in the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **26**:1038 (Nov.) 1931.

8. Riggs and Man.[1] Man and others.[2]

first group. A second group of 8 similar patients were given by mouth 30 minims (2 cc.) of compound solution of iodine U. S. P. daily for two to seven days before withdrawal of their spinal fluid. One patient, case 15, with meningovascular

Comparison of Iodine in the Blood Serum and in the Cerebrospinal Fluid

		Serum Iodine		Spinal Fluid			
Case	Age, Yr.	Total, Micrograms per 100 Cc.	Precipitable, Micrograms per 100 Cc.	Iodine, Micrograms per 100 Cc.	Aliquots, Cc.	Protein, Mg. per 100 Cc.	Comment and Results of Pneumoencephalographic Examination
				No Iodine Administered			
1	44	5.0	...	0.2	50	16.7	Progressive degenerative cerebral disorder; cortical atrophy and dilatation of ventricles
2	26	5.6	...	0.2	50	27	Injury to left frontal region of head, followed by convulsions; dilatation of left lateral ventricle
3	28	4.9	...	0.1	60	30	Psychopathic personality; low intelligence; cortical atrophy; dilatation of ventricles
4	44	8.8	...	0.4	80	11	Intellectual deterioration; cortical atrophy
5	31	5.0	...	<0.1	35	18	Chronic headaches; multiple complaints; bilateral cortical atrophy; dilatation of ventricles
6	26	6.1	5.4	0.1	25	32	Rare convulsions; queer compulsive behavior
				After Oral Administration of Compound Solution of Iodine 2 to 7 Days			
7	26	342.0	7.7	3.0	12	39	Ventricles not visualized
8	33	94.0	7.3	1.0	30	25	Repeated convulsions; bilateral cortical atrophy and dilatation of ventricles
9	55	29.0	5.9	1.6	7	48	Depressed and agitated mood with generalized tremor
10	36	121.0	5.9	2.7	9	32	Paranoid schizophrenia
11	38	303.0	5.7	11.8	30	85	Depression and failing memory; bilateral cortical atrophy; dilatation of ventricles
12	58	522.0	5.8	6.1	15	11	Cerebral arteriosclerosis; slight cortical atrophy; hydrocephalus ex vacuo
13	46	.....	6.3	3.3	35	40	Cortical scarring after head injury, with distortion of temporal horn of left ventricle; queer apathetic behavior; diabetes mellitus
14	27	.....	...	5.0*	25	42	Apathy and confusion; schizophrenia (?); ventricles not visualized
15	44	873.0	...	22 *	35	160	Meningovascular syphilis, positive Wassermann reaction
				After Administration of Desiccated Thyroid, 10 grains (0.65 Gm.) Daily for Two weeks and 15 grains (0.975 Gm.) for Third Week			
16	50	13.9	9.6	0.5	27	23	Depression; semistupor; basal metabolic rate —15 per cent; moderate cortical atrophy

* Blood was present in the spinal fluid.

syphilis was also given compound solution of iodine. Finally, 1 patient, case 16, with stupor of unknown origin, was given desiccated thyroid, 10 grains (0.65 Gm.) daily for two weeks and then 15 grains (0.975 Gm.) for one week previous to withdrawal of cerebrospinal fluid.

RESULTS

As can be seen in the table, in the spinal fluid of patients to whom no iodine was given only traces, less than 0.1 to 0.4 microgram per hundred cubic centimeters, of iodine were found in contrast to relatively large amounts, 4.9 to 8.8 micrograms per hundred cubic centimeters, in the blood serum. When sufficient inorganic iodine had been given to increase the serum iodine to as much as 522 micrograms per hundred cubic centimeters, only a very slight increase in iodine occurred in the cerebrospinal fluid. It is noteworthy that in the patient with meningitis, with a total iodine content of the serum of 873 micrograms per hundred cubic centimeters, considerable iodine entered the spinal fluid. Although there were red blood cells in the spinal fluid of this patient, the elevation in iodine was greater than would have been expected from the number of erythrocytes. Furthermore, in 2 patients high spinal fluid proteins tended to be associated with a high iodine content. Administration of desiccated thyroid to the patient in case 16 increased greatly the iodine in the serum but did not appreciably affect the iodine in the cerebrospinal fluid.

COMMENT

It can be concluded that only traces of iodine normally occur in the cerebrospinal fluid. The large aliquots of fluid used and the extreme sensitiveness of the method employed establish this point conclusively. These results confirm the observations of Klassen, Bierbaum and Curtis,[4] who used a dichromate ashing method but had less fluid for analysis.

It is noteworthy that the readily diffusible inorganic iodine did not pass in any quantity from the serum into the spinal fluid. The diffusibility of serum inorganic iodine has been previously demonstrated by Riggs, Lavietes and Man[9] in the case of red blood cell and cellophane membranes. It is clear therefore that serum inorganic iodine is prevented by some barrier from passing into the spinal fluid. The experiments of Wallace and Brodie[10] on dogs suggested such a barrier. They, however, used enormous amounts of iodine and employed one of the older macrochemical methods for iodine, thereby rendering uncertain the interpretation of their results in the case of human beings.

The protein-bound iodine, probably hormonal iodine, of serum showed no tendency to enter the spinal fluid, as might have been expected from the fact that it is not readily diffusible.

These results constitute further evidence of the unique nature of the cerebrospinal fluid. Chlorides resemble iodides so far as ionization

9. Riggs, D. S.; Lavietes, P. H., and Man, E. B.: Investigations on the Nature of Blood Iodine, J. Biol. Chem. **143**:363, 1942.

10. Wallace, G. B., and Brodie, B. B.: On the Source of the Cerebrospinal Fluid: The Distribution of Bromide and Iodide Throughout the Central Nervous System, J. Pharmacol. & Exper. Therap. **70**:418, 1940.

and diffusion are concerned; yet they are present in larger amounts in spinal fluid than in blood serum. Iodides, on the other hand, are found only in traces in the spinal fluid and, unlike the chlorides, appear to be selectively prevented from entering the spinal fluid. In contrast to the chlorides, calcium compounds behave in a manner similar to the iodides. While present in the spinal fluid in considerable quantities, calcium seems to be selectively prevented from diffusing from serum to spinal fluid in many conditions associated with hypercalcemia, in which much of the calcium is known to be in the diffusible form.[11] These observations lend support to the conception of the existence of a special blood–spinal fluid barrier.

CONCLUSIONS

Only minute amounts of iodine, less than 0.1 to 0.4 microgram per hundred cubic centimeters, are present in the spinal fluid, in contrast to relatively large amounts, 4.9 to 8.8 micrograms per hundred cubic centimeters, in the blood serum.

When the inorganic iodine of serum is increased to more than 100 micrograms per hundred cubic centimeters for days or a week, only a slight rise of 1 to 6 micrograms per hundred cubic centimeters occurs in the spinal fluid unless the protein content of the cerebrospinal fluid is also elevated.

There is, therefore, a definite barrier for iodine between the serum and the cerebrospinal fluid.

These observations add further evidence indicating the unique nature of cerebrospinal fluid as compared with other body fluids. They illustrate the peculiarly selective properties of the blood–cerebrospinal fluid barrier.

Yale University School of Medicine.

11. Merritt, H. H., and Bauer, W.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: IV. The Calcium Content of Serum, Cerebrospinal Fluid, and Aqueous Humor at Different Levels of Parathyroid Activity, J. Biol. Chem. **90**:233, 1931.

FUNCTIONAL REPRESENTATION IN THE OCULOMOTOR AND TROCHLEAR NUCLEI

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The localization of function in the cell masses of the oculomotor nucleus has not been established. While allocation of pupillary constriction to the small-celled Edinger-Westphal nucleus has been generally recognized, there is still controversy regarding the representation of functions of the extrinsic ocular muscles subserved by the third cranial nerve. Tsuchida [1] stated that there was no exact localization and that the ocular muscles received their innervation diffusely from all the cell groups. The most widely accepted view is that of Brouwer,[2] who from a review of the literature and from a single clinicopathologic observation postulated the following cephalocaudal arrangement of functional representation of the ocular muscles within the oculomotor nucleus; (*a*) sphincter pupillae; (*b*) levator palpebrarum; (*c*) superior rectus; (*d*) medial rectus; (*e*) inferior oblique, and (*f*) inferior rectus.

This scheme of segmentation had been suggested previously by Bernheimer [3] on the basis of the retrograde cell degeneration after extirpation of individual ocular muscles. There are, however, few records of physiologic investigation of the oculomotor nucleus. Hensen and Völckers [4] electrically stimulated the periaqueductal region of a dog's brain, but they admitted that their results were not altogether satisfactory because of the lack of exact methods.

From the laboratories of the Mount Sinai Hospital.

This work was aided in part by a grant from the Josiah Macy Jr. Foundation.

1. Tsuchida, U.: Ueber die Ursprungskerne der Augenbewegungen und über die mit diesen in Beziehung stehenden Bahnen im Mittel- und Zwischenhirn, Arb. a. d. hirnanat. Inst. in Zürich, 1906, no. 2.

2. Brouwer, B.: Klinisch-anatomische Untersuchung über den Oculomotoriuskern, Ztschr. f. d. ges. Neurol. u. Psychiat. **40**:152-193, 1918.

3. Bernheimer, S.: Experimentelle Studien zur Kenntnis der Innervation der inneren and ausseren vom Oculomotorius versorgten Muskeln des Auges, Arch. f. Ophth. **44**:481-525, 1897.

4. Hensen, V., and Völckers, C.: Ueber den Ursprung den Accommodationsnerven, nebst Bemerkungen über die Function der Wurzeln des Nervus oculomotorius, Arch. f. Ophth. (pt. 1) **24**:1-26, 1878.

With the Horsley-Clarke stereotaxic instrument and modern stimulator devices this difficulty may be overcome so that specific and limited areas may be stimulated with minute currents. The animal most suitable for such purposes is the monkey, not only because it can be used in the stereotaxic device but because the plan of its oculomotor apparatus is so closely related to that of man. There follows a report of a correlated functional and structural study of the oculomotor and trochlear nuclei and their roots in the monkey.

METHOD

Twenty-five monkeys (Macaca mulatta) were studied in the Horsley-Clarke apparatus by the technic described by Ranson [5] and Harrison.[6] Stimulations and lesions were made with a bipolar needle electrode having a combined diameter of 0.8 mm. A pulsating, spike-shaped current was supplied through a Dumont variable frequency stimulator. The frequency was kept constant at 250 per second. The smallest electromotive force which was necessary to produce a minimal response was 12 volts according to our instrument. This threshold was equivalent to 0.8 volt on the ordinary alternating 60 cycle sinusoidal current.

Every point explored was tested with different strengths of current. Only minimal effects were considered in final analysis. Stimulations were made under very light anesthesia induced with pentobarbital sodium or ethylcarbamate. In many instances the narcosis was so light that when the stereotaxic apparatus was removed the monkey appeared to be fully awake. Stimulations were made along vertical and horizontal planes at 0.5 to 1 mm. intervals. In 1 monkey the exploration was made in an oblique plane at an angle of 15 degrees posterior to the vertical. All the monkeys withstood the operations and recovered quickly. In 4 of the animals lesions were made at designated points with electrocoagulation currents of 3 milliamperes for fifteen to thirty second intervals. The monkeys were then observed daily for oculomotor defects. Pupillary reactions were studied cinematographically under infra-red illumination and controlled light stimulation by Dr. Otto Lowenstein, at New York University.

For histologic studies, 14 monkeys were killed by an overdose of sodium pentobarbital. The points of stimulation were identified and checked against horizontal and vertical wires passed through arbitrary points. In 7 monkeys stimulations were made along both vertical and horizontal planes so that each needle tract served as an anatomic gage against the other in terms of the right-angled coordinate. Allowances were made for shrinkage after embedding in pyroxylin. Serial sections were made of each brain stem and stained by the Weil, hematoxylin and eosin and Nissl methods.

RESULTS

Effects of Stimulation.—With small currents discrete unilateral oculomotor responses were obtained by stimulating the regions of the oculomotor nucleus and roots.

When the electrode was moved down dorsoventrally in the vertical plane of the stereotaxic instrument, the first of the oculomotor responses

5. Ranson, S. W.: On the Use of the Horsley-Clarke Stereotaxic Instrument, Psychiat. en neurol. bl. **38**:534, 1934.

6. Harrison, F.: Modification in Technic for Use of the Horsley-Clarke Stereotaxic Instrument, Arch. Neurol. & Psychiat. **40**:563-565 (Sept.) 1938.

obtained was ipsilateral pupillary constriction. With slightly greater currents the constriction was bilateral, but was usually more marked on the side of stimulation. Bilateral miosis was also obtained from other areas, such as the regions of the pretectum and posterior commissure, as described by Ranson and Magoun [7] and Magoun and Ranson,[8] and from the ventral portion of the central tegmental fasciculus. The miosis obtained from the central tegmental fasciculus in the pons is part of the lid closure reaction, in which the eyelids close and the eyeballs roll up in association with pupillary constriction.

Ventral to the focus for pupillary constriction was that for downward movement of the ipsilateral eyeball. In 1 monkey conspicuous bulging of both irises was observed on stimulation of a point at the midvertical and midsagittal planes of the body of the oculomotor nucleus. The focus was 1 mm. below that for pupillary constriction. The bulge in the iris was prominent during the entire period of stimulation and was greatest at the pupillary margin. When the current was stopped the bulge receded sharply. There was no associated convergence movement, and unless more than threshold current was used there was no pupillary constriction. It is presumed that the bulge in the iris was due to contraction of the ciliary muscle, causing the lens to become more globular and to move forward, which pushed the iris anteriorly.

The next ventral point yielded downward and inward movements. Again, this response was ipsilateral, and with increase in voltages at the same point of stimulation other ipsilateral ocular movements appeared, in the following sequence: (*a*) 13 volts, downward and inward; (*b*) 14.5 volts, inward; (*c*) 17.5 volts, inward and upward, and (*d*) 25 volts, inward and upward plus retraction of the lid. Thus by increasing the current at any one point it was possible for one to predict the response of adjacent or deeper structures. The downward and inward motion seemed to be the resultant action of the inferior and the internal rectus muscle. At times this oblique movement had an element of extorsion, but never the intorsion produced by the action of the superior oblique muscle, innervated by the fourth cranial nerve. The direction of the torsion could readily be detected by observing the movement of radiating conjunctival vessels.

One millimeter below the focus for downward and inward movement was that for pure adduction. This individual inward movement was ipsilateral and was seemingly the strongest of all effects produced by stimulation in this region of the brain stem. When the electrodes were

7. Ranson, S. W., and Magoun, H. W.: The Central Path of the Pupillo-Constrictor Reflex in Response to Light, Arch. Neurol. & Psychiat. **30**:1193-1202 (Dec.) 1938.

8. Magoun, H. W., and Ranson, S. W.: The Central Path of the Light Reflex: A Study of the Effect of Lesions, Arch. Ophth. **13**:791-811 (May) 1935.

within 0.2 mm. of the midline and the current was strong enough, bilateral sharp inward rotation of the eyes occurred, but this could be distinguished from the slower bilateral convergence movements elicited from other regions.

The next ventrally situated point yielded inward and upward movement. Again, this was ipsilateral and probably the resultant action of the internal and the superior rectus muscle. On further sinking of the electrode pure upward movement of the eyeball was elicited, and 0.5 to 1 mm. below this center stimulations yielded elevation of the superior eyelid.

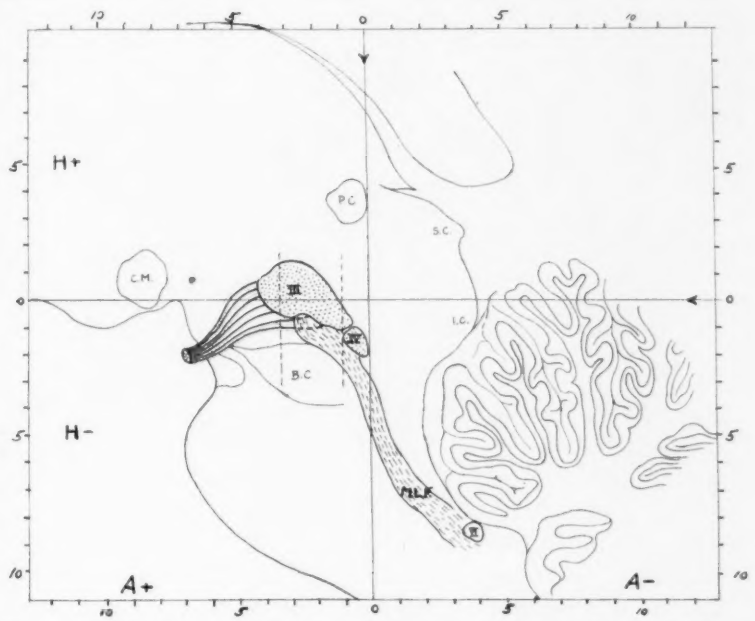

Fig. 1.—Projection drawing of a sagittal section through the brain stem of a monkey 0.5 mm. lateral to the midplane. The arrows on the zero vertical and zero horizontal lines indicate direction of stimulation. The scale on each side is expressed in millimeters. *III* indicates oculomotor nucleus and projected roots; *IV*, trochlear nucleus; *VI*, abducens nucleus; *B.C.*, brachium conjunctivum; *C.M.*, corpus mamillare; *I.C.*, inferior colliculus; *M.L.F.*, median longitudinal fasciculus; *P.C.*, posterior commissure, *S.C.*, superior colliculus; *A* + vertical planes anterior to the zero frontal plane; *A* —, vertical planes posterior to the zero frontal plane; *H* +, horizontal planes above the zero horizontal plane; *H* —, horizontal planes below the zero horizontal plane. *L* (in text) indicates planes lateral to the midsagittal plane.

From still deeper zones trochlear nucleus effects were noted, i. e. intorsion of the contralateral eye. At this point slightly greater than liminal currents yielded upward movement of the ipsilateral globe, eleva-

tion of the upper lid and intorsion of the opposite eye, a result demonstrating that the cells controlling retraction of the lid are situated in the most caudal and ventral portion of the oculomotor nucleus, adjacent to the trochlear nucleus. In this plane pupillary constriction was obtained only from the posterior commissure, never from the caudal portion of the oculomotor or the trochlear nucleus. Stimulation of the trochlear nerve roots produced ipsilateral intorsion movements.

The reactive area for ipsilateral oculomotor responses was 3 to 4 mm. in the vertical plane of the instrument, 5 to 6 mm. in the horizontal plane (fig. 1) and 0.5 to 1.5 mm. lateral to the midline. At the more

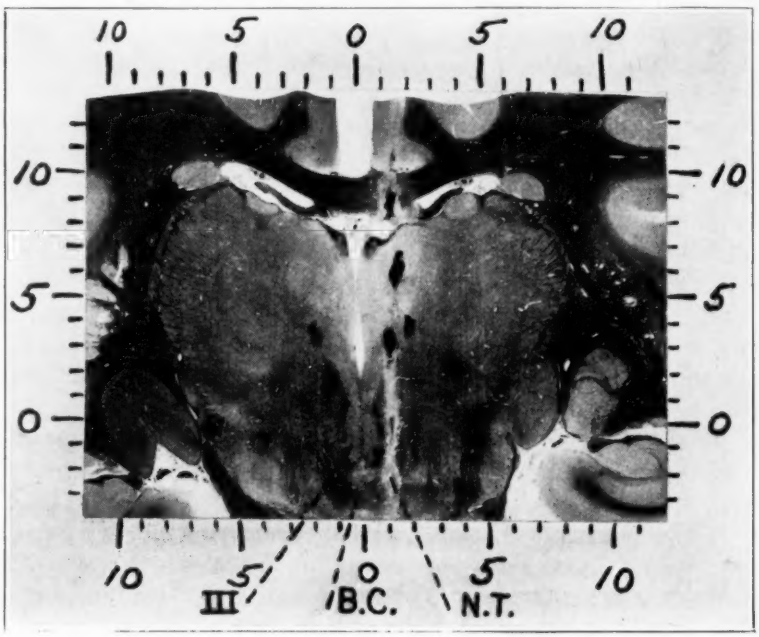

Fig. 2.—Photograph of a frontal section through the rostral portion of the oculomotor nucleus at $A + 3.2$, as indicated in the sagittal section (fig. 1). The The needle tract (*N.T.*) is 1 mm. lateral to the midline. Abbreviations in this figure and in figure 3 are the same as those used in figure 1.

rostral and dorsal coordinates pupillary constriction and downward and inward movements of the homolateral globe were obtained (fig. 2); from the caudal and ventral region inward and upward motions of the globe and retraction of the upper eyelid were elicited (fig. 3).

Point stimulations carried out during withdrawal of the electrodes yielded the same oculomotor responses as those described when the electrodes were moved downward, but in reverse order, results which corroborated the foregoing observations. Stimulations in the horizontal

plane also confirmed the results obtained in the vertical planes. With the electrodes moving at 1 mm. intervals in a rostral direction, the following successive ipsilateral ocular movements were obtained: (1) retraction of the upper lid; (2) upward movement; (3) upward and inward movement; (4) inward movement; (5) inward and downward movement;

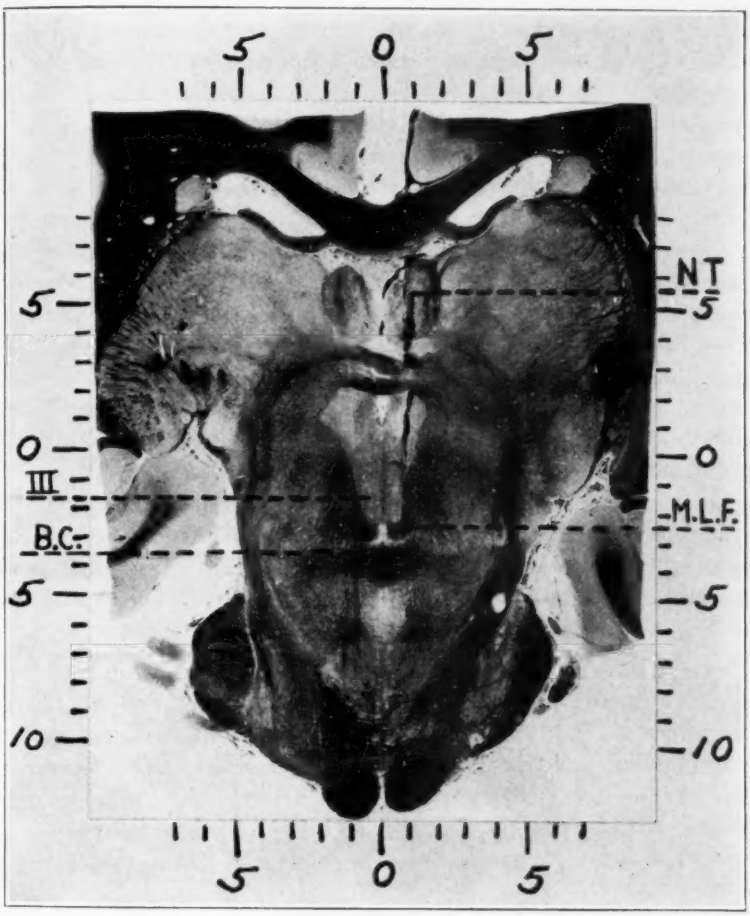

Fig. 3.—Photograph of a frontal section through the caudal portion of the oculomotor nucleus at $A + 1$ in the sagittal projection, with the needle tract running 0.4 mm. lateral to the midline.

(6) downward rotation of the globe; (7) pupillary constriction (often bilateral). A precise center for action of the inferior oblique muscle was difficult to elicit. In 4 experiments definite extorsion (action of the inferior oblique muscle) of the ipsilateral eye was observed by stimulation of the rostral zones of the oculomotor nerve roots. In 1

experiment a contralateral inferior oblique muscle effect was obtained. In order to produce extorsion movements, however, higher voltages were necessary.

Effect of Lesions.—Small electrolytic lesions were made with direct currents of 1 to 2 milliamperes directed for fifteen seconds to a focus in the dorsal and rostral region of the oculomotor nucleus. This was at a point just above that for downward movement of the globe (A + 2.5, L 0.5, H 0) where stimulation yielded pupillary constriction. As soon as the monkey recovered from the anesthetic, it showed on the side of the lesion (1) an enlarged pupil, which constricted slightly to light and closure of the lids and (2) defective downward movement of the globe when in the abducted position. There was no ptosis or other ocular muscle defects. The pupillary disturbance lasted over ninety-nine days, while the impairment of action of the inferior rectus muscle lasted four days.

Small electrolytic lesions were also made in the caudal and ventral region, in the "tail" of the oculomotor nucleus. This was at a point (A + 1.0, L 0.7, H — 3.5) where stimulations yielded ipsilateral upward and inward movement of the globe with retraction of the upper eyelid and action of the contralateral superior oblique muscle. Such a localized lesion produced partial ptosis of the superior eyelid, which lasted three days.

An electrolytic lesion in the oculomotor root fibers, converging from the nucleus toward the base of the peduncle, resulted in partial weakness of all the intrinsic and extrinsic ocular muscles supplied by the ipsilateral third cranial nerve without dissociation. This lasted many months.

COMMENT

According to our experiments, the dorsoventral and rostrocaudal arrangement of the functional representation of the ocular muscles in the oculomotor and trochlear nuclei of the monkey is as follows: (1) sphincter pupillae (usually bilateral responses); (2) inferior rectus; (3) ciliary (?); (4) inferior oblique (?); (5) internal rectus; (6) superior rectus; (7) levator palpebrarum, and (8) superior oblique (contralateral).

Except for movements of the superior oblique muscle, the actions of the extrinsic ocular muscles are purely homolateral. The functional pattern in the oculomotor nucleus which we present is considerably at variance with that which Brouwer [2] conjectured as existing in man. The chief corrections are in the localization of movements of the upper eyelid and the vertical rotations of the globe. On the basis of casuistic and some pathologic data from the literature and from 1 of his own cases, Brouwer [2] reached the conclusion that foci for the upward movement of the eyeball and superior lid were situated in the dorsal portion of

the oculomotor nucleus. The evidence which he cited, however, is hardly convincing. Bach,[9] who made clinical, pathologic, anatomic and experimental observations on man and animals, found that centers for the upward movements of the globe and superior lid were located in the more ventral and caudal portion of the oculomotor nucleus. Von Monakow's [10] clinicopathologic studies on man yielded similar conclusions. Our experimental data confirm the observations of Bach and von Monakow. At least in the monkey the centers for elevation of the globe and the upper lid are situated in the caudal and ventral portion of the oculomotor nucleus just rostral to the nucleus trochlearis. The focus for downward movement of the globe is localized to the rostral and dorsal portion of the oculomotor nucleus just ventral to the point for pupillary constriction.

The ocular movements described may be obtained in all the vertical planes running through the oculomotor nucleus, but in the order described, i. e., the most dorsal stimulations yielding downward and the most ventral upward movements. The best downward motions were observed in the rostral vertical planes. No downward rotation, however, could be elicited from the most caudal vertical planes. On the basis of these observations it would appear that the functional arrangement within the nucleus is somewhat comma shaped. In the head, or the rostral end, are situated the centers for pupillary constriction and downward movement of the globe; in the body is the focus for action of the internal rectus muscle, while in the tail, or the caudal zone, next to the trochlear nucleus, are the centers for upward movement of the globe and superior eyelid. The arrangement also seems to have a lamellar character in the horizontal plane. This lamellar distribution may be due to the arrangement in the oculomotor rootlets, which emerge from the nucleus to run in a ventral and rostral direction (fig. 3). The exact localization of the center for pupillary constriction has not been considered in detail in this investigation. This problem had already been studied in cats by Ranson and Magoun,[7] Magoun and Ranson [8] and Benjamin.[11] From our experiments it appears that the center for the sphincter pupillae in the monkey is represented in the most rostral and dorsal portion of the oculomotor nucleus, probably in the small cells of the Edinger-Westphal nucleus. An interesting observation is the bulging of the iris on stimulation of a point near the foci for pupillary constriction and action of the inferior rectus muscle. The bulge is presumably

9. Bach, L.: Zur Lehre von den Augenmuskellähmungen in den Störungen der Pupillbewegung, Arch. f. Ophth. **47**:339-386 and 551-630, 1939.

10. von Monakow, C.: Gehirnpathologie, ed. 2, Vienna, A. Hölder, 1905, p. 103.

11. Benjamin, J. W.: The Nucleus of the Oculomotor Nerve with Special Reference to Innervation of the Pupil and Fibers from the Pretectal Region, J. Nerv. & Ment. Dis. **89**:294-310, 1932.

due to contraction of the ciliary muscle, which, in turn, causes the lens to become more spherical and thus push the iris anteriorly.[12] That this action may be obtained without convergence or pupillary constrictor movements proves that the ciliary muscle has a distinct localization in the oculomotor nucleus.

SUMMARY

Electric stimulations and lesions were made in the oculomotor and trochlear nuclei of monkeys. These experiments indicate that individual ocular muscles are functionally represented within the ipsilateral oculomotor nucleus, while the superior oblique muscle is governed by the contralateral trochlear nucleus. The dorsoventral and rostrocaudal arrangement of functional representation of the ocular muscles is as follows: (1) sphincter pupillae; (2) inferior rectus; (3) ciliary (?); (4) inferior oblique (?); (5) internal rectus; (6) superior rectus; (7) levator palpebrarum; (8) superior oblique (contralateral).

Mr. M. Grabiner gave technical assistance.

1165 Park Avenue.

12. Hensen, V., and Völckers, C. V.: Ueber die Accommodationsbewegung der Choroidea im Auge des Menschen, des Affen und der Katze, Arch. f. Ophth. (pt. 1) **19**:156-162, 1873.

FATALITIES FOLLOWING ELECTRIC CONVULSIVE THERAPY

REPORT OF TWO CASES, WITH AUTOPSY

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The present widespread use of electric convulsive therapy in psychiatry prompts one to analyze carefully occasional cases of fatality from its use. Cerletti,[1] citing his original work with Bini, stated that although thousands of convulsions have been produced in patients, no deaths have occurred. In a survey of this situation by the United States Public Health Service [2] in October 1941, 4 such deaths were reported, which is a rate of 0.5 per thousand of the total number of patients treated by this method. As far as we have been able to ascertain, throughout the United States up to June 1942 10 deaths, including the 2 in our experience, have occurred. Of these 10 fatalities, the cause of 2 was immediate respiratory failure, the data on 1 were unknown and the electric convulsive therapy served as a contributing cause of the others. The distribution of the cases is shown in the accompanying table.

In this paper we wish to discuss 2 cases of death of patients receiving electric convulsive therapy.

REPORT OF CASES

CASE 1.—A man aged 57 with a depressive psychosis was given electric shock therapy, with the induction of twelve grand mal and one petit mal seizure. A careful preliminary preshock series of investigations was made, including routine examination by a cardiologist, who reported that the heart was organically intact

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Read at the Sixty-Seventh Annual Meeting of the American Neurological Association, Chicago, June 4, 1942.

1. Cerletti, U.: Annotazioni sull' elettroshock, Wien. med. Wchnschr. **90**: 1003, 1940.

2. Kolb, L., and Vogel, V. H.: The Use of Shock Therapy in Three Hundred and Five Mental Hospitals, Am. J. Psychiat. **99**:90 (July) 1942.

Data on Cases of Death Following Electric Shock Treatment

Age, Yr.	Number of Electric Shock Treatments Given	Diagnosis	Date and Cause of Death	Autopsy Observations
		State Hospital Group		
45	62 (over a period of 5½ months, to July 1941)	Schizophrenic reaction	August 1941; cardiac failure	To be reported in literature
29	19 "electric stimulating treatments," without single grand mal reaction; previous insulin treatment	Manic-depressive psychosis, with several previous attacks	Status epilepticus 3 days after last treatment; medical examiner made diagnosis "coronary thrombosis and influenza" on death certificate	Autopsy not permitted
56	22 brief subconvulsive treatments and 30 convulsive treatments	Manic-depressive psychosis, mixed type	3 months after treatment, as result of acute respiratory infection and septicemia	Permission for autopsy not obtained
75	3 electric shock treatments with curare, with improvement	Manic-depressive psychosis, depressed type; advanced generalized arteriosclerosis	After third treatment cardiac fibrillation, probably ventricular, with immediate death	Advanced cerebral arteriosclerosis; chronic leptomeningitis; atherosclerosis of aorta; acute passive congestion of the lungs, liver and spleen
		Private Hospital Group		
79	6 electric shock treatments	Manic-depressive psychosis, fifth attack; patient discharged as improved; later operation for cataract, with return of symptoms	4 months after last electric shock treatment, with cardiac failure	Reports not available at present
58	1 treatment	Schizophrenic reaction	Death after first treatment "due to involvement of central nervous system and preceded by respiratory failure"	Permission for autopsy not obtained
?	Data not obtainable			
50	1 treatment	Manic-depressive reaction	After grand mal seizure; patient never regained consciousness	Reports not available at present
		Cases Reported in This Paper		
57	13 electric shock treatments given, with 12 grand mal and 1 petit mal seizure	Agitated depression	April 3, 1941, 1 hr. 35 min. after grand mal reaction; coronary thrombosis	Coronary occlusion and myocardial infarction; small areas of cortical devastation; diffuse degeneration of cortical nerve cell; astrocytic proliferation
57	3 treatments, with 2 petit mal and a terminal grand mal seizure	Manic-depressive psychosis, manic type	Jan. 11, 1942, following third shock and first grand mal seizure with immediate respiratory failure	Small areas of recent necrosis in cortex, hippocampus and medulla; astrocytic proliferation

and that the electrocardiogram revealed nothing abnormal. The average dose of electrical current was 85 volts and 900 milliamperes administered for a duration of fifteen-hundredths second. The treatments were given biweekly. After the last grand mal convulsion the patient complained of pain suggesting angina pectoris and died within one and one-half hours.

Autopsy Observations.—The main pathologic changes were observed in the heart and brain. The heart was slightly hypertrophied and showed a soft, moist, discolored area in the upper half of the anterior wall and interventricular septum. The horizontal branch of the left coronary artery was firm and thickened and showed several elevated and partly calcified plaques. The descending branch was converted into a rigid, calcified tube with many narrowing plaques. Its

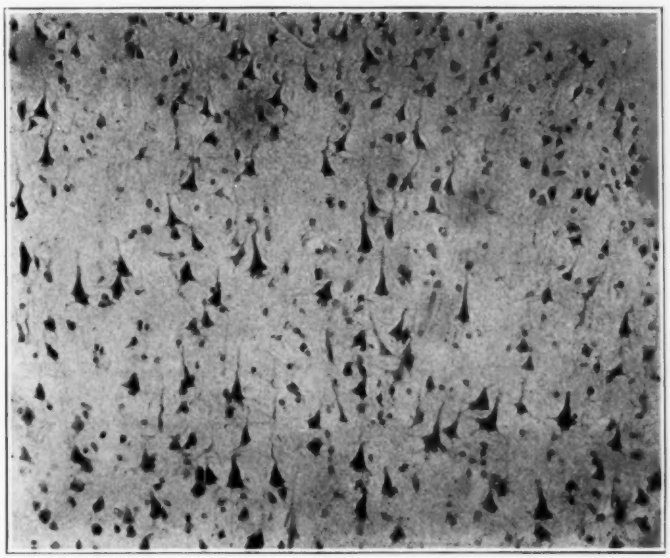

Fig. 1 (case 1).—Irregular cortical architecture; sclerosed nerve cells; ghost cells. Nissl stain.

upper part was impervious for a distance of about 4 cm.; the lumen was occluded by adherent brownish thrombotic masses, which had been deposited on the surface of coalescing ulcerated plaques.

The brain appeared normal in shape, size and weight. The arteries were thin walled and free from sclerosis. Sections through the brain revealed only one isolated petechia, lying in the subcortical white matter of the left occipital lobe.

Microscopic Study.—Sections taken from the myocardium showed a number of small, old cellular scars in various portions. The area displaying grossly the diminished firmness exhibited several spots of poor stainability and splitting and tortuosity of muscle fibers; nuclei were in part unstainable, while others appeared dark and shrunken.

Blocks taken from various areas of the brain were examined histologically by numerous methods.[3] Under low magnification the brain tissue appeared fairly normal at first sight, but closer examination revealed a number of changes,

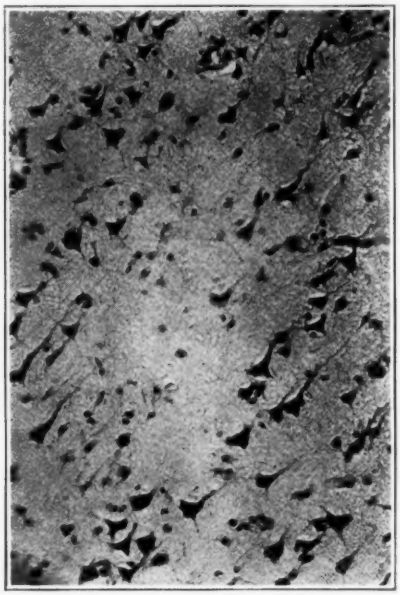

Fig. 2 (case 1).—Circumscribed area of recent cortical necrosis. Nissl stain.

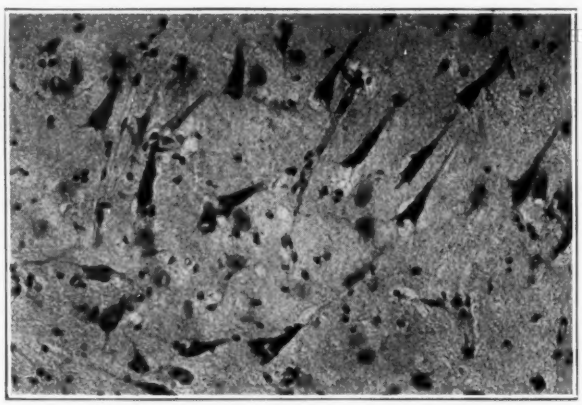

Fig. 3 (case 1).—Astrocytic proliferation in the hippocampus. Nissl stain.

3. In both cases frontal, parietal, temporal and occipital regions of the cortex, the interbrain, the basal ganglia, the thalamus, the substantia nigra, the pons, the cerebellum and the medulla were examined; the staining methods of Nissl, Penfield, Bielschowsky, Holzer, Río Hortega, Cajal and Loyez were applied, in addition to the use of hematoxylin and eosin and stains for fat.

predominantly located in the frontal and temporal lobes. Several small areas of devastation appeared to be entirely devoid of nerve cells or contained some ghost cells. In some of these areas the glia showed a certain activity; there were a few swollen astrocytes and *Gliarasen;* in addition, a limited number of proliferated microglia cells were occasionally observed, their processes containing tiny granules of fat in some instances. Furthermore, there was diffuse degeneration of nerve cells in the cortex, which was most pronounced in the tops of the convolutions. This degeneration consisted chiefly in shrinkage or sclerosis of cells, which appeared dark and elongated with tortuous dendrites. Occasionally there was slight vacuolation of the cytoplasm. Elsewhere, paleness or ischemic degeneration of scattered nerve cells was seen, the neurons being faintly stained, slender and triangular, with pale, triangular nuclei. Owing to these lesions, the architecture of the cortex appeared irregular in places. The number of astrocytes was diffusely increased in a slight to moderate degree in the upper and deep cortical layers. The hippocampus showed ischemic changes in scattered nerve cells and small areas with swollen astrocytes and absence of nerve cells. There was also an increase in the number of astrocytes in the polymorphic cell layer of the hippocampus. Other regions of the brain showed the changes described to a far less degree. The senile lipoid pigment in the neurons was perhaps more prominent than normal for the age of the patient. Senile plaques and fibrillary alteration were not seen. No demyelination was noted. Arteries and arterioles were practically free from sclerosis. Small accumulations of perivascular pigment were occasionally seen in the white matter. There was no noteworthy damage to the neurofibrils.

Case 2.—A man aged 57 was treated by electric shock for a manic reaction. He died after the third treatment, immediately after the first grand mal seizure. Treatments were given at weekly intervals, and during the first two petit mal attacks the patient experienced respiratory difficulties after the seizure. It was thought that these reactions were due to administration of curare. Oxygen was administered, as well as prostigmine methylsulfate. In the last treatment the grand mal convulsion was produced with 85 volts and 900 milliamperes, given for fifteen-hundredths second. Respiration immediately ceased and, despite artificial respiration, administration of the usual stimulants and heroic measures, was never reestablished.

Autopsy Observation.—No satisfactory explanation of the sudden death was obtained.

Microscopic Study.—Examination of the organs of the body was noncontributory. Microscopic changes in the brain were present throughout the cortex and were not notably accentuated in the frontoparietal region, through which the electric current is supposed to have passed. The cortical architecture was fairly well preserved. However, there were areas within which a number of nerve cells were pale or showed frank ischemic change. This as a rule was so pronounced as to be recognizable under low magnification. No area with loss of all the nerve cells was seen. Scattered single nerve cells throughout the cortex had undergone similar changes. A few nerve cells in Sommer's sector of the hippocampus showed early ischemic change.

Glial reactions were slight. However, occasional small rod cells were visible in involved areas, and swelling of the astrocytes was discernible. Glial changes were more noticeable in the hippocampus, particularly in the polymorphic layer. In this region the nerve cells appeared to be fairly well preserved but were

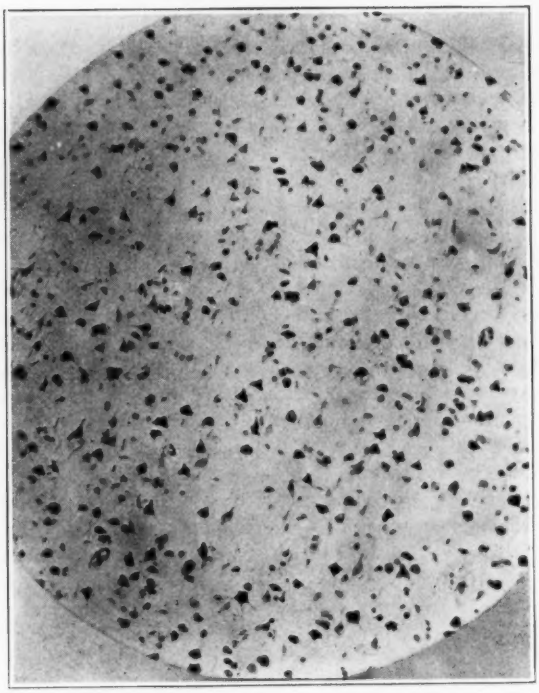

Fig. 4 (case 2).—Irregular cortical architecture; dropping out of neurons; rod cells. Nissl stain.

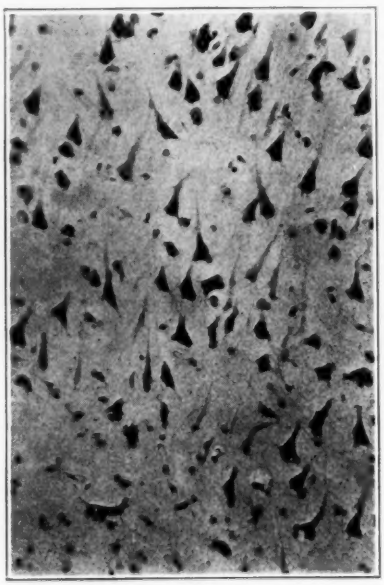

Fig. 5 (case 2).—Recent ischemic changes in nerve cells of the hippocampus. Nissl stain.

somewhat reduced in number, a few degenerating neurons being seen. Many astrocytes, with pale, enlarged nuclei and swollen cytoplasm, were visible with the Nissl stain. In Cajal stains their number was estimated to be at least twice the normal.

In the thalamus occasional nerve cells showed very pale, poorly defined and vacuolated cytoplasm, with somewhat distorted nuclei and in some instances breaking up of the nucleoli. Occasional swollen astrocytes were seen, and small glia nodules as well; neuronophagia was noted in rare instances.

In the basal ganglia the large cells of the striatum were in fair to good condition. The small cells showed occasional satellitosis and changes similar to

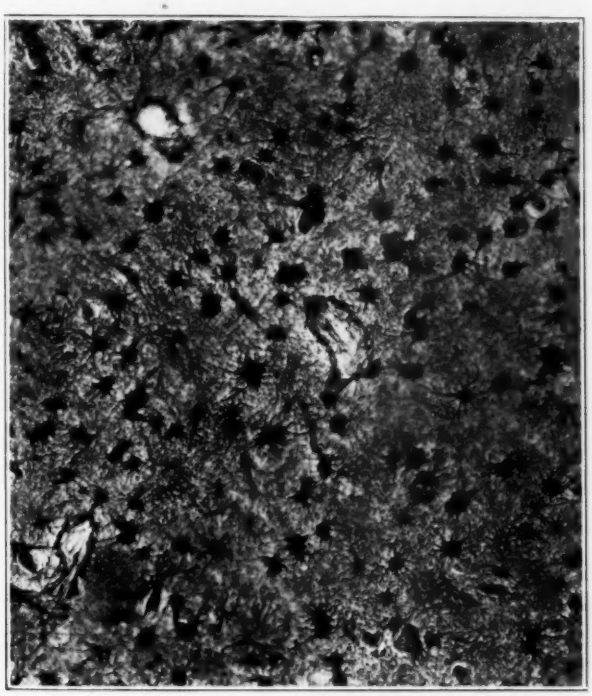

Fig. 6 (case 2).—Astrocytic proliferation in the hippocampus. Cajal stain.

those in the thalamus. A few ghost cells and some swelling of astrocytes were observed. The changes had a patchy distribution, with areas in the very vicinity which appeared normal. The globus pallidus was in good condition, with occasional traces of swelling of the vascular endothelium and very slight round cell infiltration about a small number of veins.

The medulla was normal in most areas. However, the dorsal vagus nucleus, particularly on the left, showed occasional pale cells with satellitosis and ghost cells with neuronophagia. Enlarged glial nuclei and small *Gliarasen* were seen in places. Similar, but less pronounced, glial activity was observed in the substantia reticularis and in the nucleus arcuatus.

All other areas examined were practically normal except for slight, almost negligible, changes of the types already described.

COMMENT

The death in the first case was undoubtedly due to the severe coronary disease with resulting very early infarction of the myocardium, superimposed on older myocardial damage. Death would probably have occurred at any rate within a short time, independent of the electric shock therapy. However, the treatment may have accelerated the death. It may well be assumed that the collateral circulation and the blood supply of the heart were sufficient while the patient remained quietly in bed; the electric shock probably was an increased burden on the heart, leading to failure of coronary blood supply. It is known that electric shock of any kind may involve the coronary circulation, and may even cause symptoms of angina pectoris (Alexander [4] and Huellstrung [5]). While in the case of a patient with a normal heart this would not come into question on application of the customary electric shock treatment, with its weak current, it is easily understood that a patient with severe sclerosis of the coronary arteries would not be able to endure the shock.

The explanation of the fatal outcome in the second case meets with great difficulties. The changes in the brain cannot be considered directly responsible for the death. They are indicative of some damage suffered by the brain during the shock treatment, but they do not answer satisfactorily the question of the cause of death.

It has been known for a considerable time that different persons react differently to electric trauma. The literature furnishes examples of persons having been killed by currents of 46 volts and 1/100 ampere (Welz [6]). Thus, one might assume an individually increased susceptibility to slight electric trauma.

Furthermore, it must not be forgotten that the grand mal seizure may lead to apnea, "since it produces oxygen lack which depresses the respiratory center, and it also leaves the patient in a comatose state, with a variable degree of airway obstruction due to spasm or collapse of the pharynx, larynx, lips and tongue," as asserted by Brill and Kalinowsky.[7] These authors stated recently that no fatal accident has yet been reported and that the only danger of the electric shock therapy lies in the possibility of postconvulsive respiratory arrest; they reported a case of serious but nonfatal asphyxia following a grand mal attack during electric shock treatment.

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4. Alexander, L.: Neuropathological Aspects of Electric Injuries, J. Indust. Hyg. & Toxicol. **20**:191, 1939.

5. Huellstrung, P.: Starkstromunfall als Ursache von Angina pectoris, Klin. Wchnschr. **13**:409, 1934.

6. Welz, A.: Starkstromtod und Hirntod, Virchows Arch. f. path. Anat. **305**: 646, 1940.

7. Brill, H., and Kalinowsky, L.: Asphyxial Episodes and Their Prevention in Electric and Other Convulsive Therapies, Psychiatric Quart. **16**:351, 1942.

We may well assume that the course of events was similar in the present case, with its sudden onset of respiratory failure after the attack. Wortis and his associates [8] have recently stated that electrically produced convulsions inhibit oxygen uptake, a statement which also agrees with our explanation.

Our assumption appears all the more justified in that lesions in the medulla were observed. It must be admitted that they were slight and per se probably without great significance. They do show, however, that the medullary centers reacted in an unusual fashion to the electric shocks. (Even after his two petit mal seizures the patient had respiratory trouble.[9]) These centers may have failed, accordingly, in the grand mal seizure provoked by the last electric shock.

The histologic changes in the brain are interesting from several points of view. As not only in the first case but also in the second glial reactions were exhibited which must be considered older than a few minutes, we are entitled to assume that not the grand mal seizure but the action of the electric current on the brain produces such glial changes, unless the petit mal seizure is the cause, which is unlikely. Histologically, well discernible lesions in the neurons may develop experimentally within a few minutes (Heilbrunn and Liebert [10]), but according to all experiences proliferative changes in the glia require more time. While, therefore, the changes in the nerve cells may in part be a sequel of the last grand mal seizure, the glial reactions are certainly older and must have been produced by the former shocks, which were followed only by petit mal seizures.[11] Corresponding conclusions must be drawn regarding the first case. Here, however, the great number of grand mal seizures over a long time renders statements as to the genesis of the histologic lesions more difficult. All the lesions observed in the brain in both cases were brought about by the electric shock treatment, partly, in our opinion, in connection with the seizures produced by that treatment; neither the mental condition nor the pathologic changes elsewhere in the body can be made responsible for these lesions.

The histologic lesions in the brain are not to be considered serious. Certainly, many of the changes were reversible. The bulk of the parenchyma was left intact. The changes described were in no instance incompatible with longer duration of life, and they were by no means

8. Wortis, S. B.; Shaskan, D.; Impastato, D., and Almansi, R.: The Effects of Electric Shock and Some Nerve Drugs, Am. J. Psychiat. **98**:354, 1941.

9. The role played by curare appears doubtful.

10. Heilbrunn, G., and Liebert, E.: Biopsies of the Brain Following Artificially Produced Convulsions, Arch. Neurol. & Psychiat. **46**:548 (Sept.) 1941.

11. The question whether one epileptic seizure may produce histologically discernible changes in nerve cells in the human brain cannot be definitely answered and will not be discussed in this paper.

likely to interfere seriously with the normal function of the central nervous system. One would not be justified in suggesting rejection of electric shock therapy on account of the fatalities reported; these fatalities should only arouse doubts as to its applicability in the treatment of elderly patients, particularly if there is evidence of cardiac involvement.

In each of the 2 cases reported a cardiologist was called in consultation, complete collaborative electrocardiograms were made and on the basis of negative evidence treatment was approved. The indications and contraindications for this type of drastic therapy must always be carefully evaluated. We should advise repeated check-ups by the cardiologist during the progress of the treatment.

The stimulation of the astrocytes in both cases was considerable and recalls what Weil and Liebert [12] described in their neuropathologic study of cases of psychoses in which metrazol was used.

The changes were not limited to the pathway of the electric current, although it must be admitted that they were perhaps slightly more marked in this region, particularly in the first case; the differences, however, were so little pronounced as to be almost negligible.

The cerebral lesions are probably due both to direct action of the current on the parenchyma (diffuse lesions) and to circulatory disturbances brought about by the current (focal lesions) in wide areas of the brain (Morrison, Weeks and Cobb [13]; Alexander [14]; Echlin [15]). The cerebral damage in our case was not much different from that seen in animal experiments (Neubuerger, Whitehead, Rutledge and Ebaugh [16]).

Different species of animals seem to react in a different fashion to electric shock. While we saw parenchymal changes of a slight degree as a predominant feature in dogs, Alpers and Hughes [17] observed hemorrhages in the brain and meninges in cats.

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12. Weil, A., and Liebert, E.: Neuropathologic Study of Six Cases of Psychoses in Which Metrazol Was Used, Arch. Neurol. & Psychiat. **44**:1031 (Nov.) 1940.

13. Morrison, R.; Weeks, A., and Cobb, S.: Histopathology of Different Types of Electric Shock in Mammalian Brains, J. Indust. Hyg. & Toxicol. **12**: 324, 1930.

14. Alexander, L.: Electric Injuries of the Nervous System, Arch. Neurol. & Psychiat. **47**:179 (Jan.) 1942.

15. Echlin, F. A.: Vasospasm and Focal Cerebral Ischemia: Experimental Study, Arch. Neurol. & Psychiat. **47**:77 (Jan.) 1942.

16. Neubuerger, K. T.; Whitehead, R. W.; Rutledge, E. K., and Ebaugh, F. G.: Pathologic Changes in the Brains of Dogs Given Repeated Electrical Shocks, Am. J. M. Sc. **204**:381 (Sept.) 1942.

17. Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, Arch. Neurol. & Psychiat. **47**:385 (March) 1942.

SUMMARY

Two fatalities following electric shock treatment are reported. In the first case death was due to coronary occlusion and myocardial infarction. In the second case the general autopsy observations were without significance. It was assumed that the fatal outcome was due to postconvulsive respiratory arrest. Both cases showed rather widespread, but not serious, histologic changes in the brain. The pathogenesis and the significance of the histologic changes are discussed. The importance of repeated careful investigations of cardiac function in patients who are considered for electric shock treatment is emphasized.[18]

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18. The articles by B. J. Alpers and J. Hughes (The Brain Changes in Electrically Induced Convulsions in the Human, J. Neuropath. **1**:173-180, 1942) and by G. Heilbrunn and A. Weil (Pathologic Changes in the Central Nervous System in Experimental Electric Shock, Arch. Neurol. & Psychiat. **47**:918-930 [June] 1942) had not come to our attention when this paper was completed.

ACUTE SYPHILITIC ANTERIOR POLIOMYELOPATHIC SYNDROME

REPORT OF A CASE

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In rare instances syphilis has been reported as responsible for the origin of the syndrome of acute anterior poliomyelitis. Another case is here added to the list.

REPORT OF CASE

A white man aged 29 was admitted to the Johns Hopkins Hospital (service of Dr. W. T. Longcope) on March 22, 1942, complaining of inability to swallow and weakness of both legs. The illness began a fortnight earlier with sore throat and temporary double vision. Later he had difficulty in swallowing (fluids regurgitating through the nose) and increasing paralysis of the legs. A lumbar puncture (done at another hospital on the day before admission) revealed a cell count of 100 cells (small mononuclears) per hundred cubic centimeters of fluid and an increase of globulin. It was believed that he had acute anterior poliomyelitis, and he was sent to the isolation ward of the Johns Hopkins Hospital.

His earlier history was without significance except for gonorrhea at the age of 29. He denied having had other venereal infections. He was married and had 2 healthy children.

Physical examination revealed pronounced dysphagia, flaccid paralysis of both lower extremities, moderate weakness of the muscles of the upper extremities and absence of knee and ankle jerks. The pupillary reactions, the sphincters and the superficial reflexes were at that time normal.

Laboratory tests revealed slight leukocytosis (10,700 cells) and strongly positive Wassermann reactions of the blood and cerebrospinal fluid.

Though an orthopedic consultant favored the diagnosis of acute anterior poliomyelitis, the internists thought it probable, in view of the serologic reactions, that syphilis was responsible for the whole clinical picture, especially as the age of the patient, the season of the year, the insidious onset of the illness, the absence of pain and the peculiar distribution of the paralyses were out of accord with the diagnosis of ordinary poliomyelitis.

Five days after admission, the patient became unable to void urine and had to be catheterized regularly. Slight hypesthesia of the left thigh developed. The disturbance of bladder function, as well as the hypesthesia, favored the diagnosis of neurosyphilis rather than that of Heine-Medin disease. Moreover, absence of the virus of poliomyelitis from the feces was proved by inoculation of monkeys by Dr. H. A. Howe.

Under intensive antisyphilitic therapy (bismosol, potassium iodide and intravenous injections of mapharsen) rapid improvement occurred. By March 29 the patient could swallow, and tube feeding was discontinued. Muscular strength increased later, and the cell count of the spinal fluid fell to 6 cells per cubic millimeter. By May 23 the symptoms had largely disappeared. Though there

was still some weakness of the lower extremities, it seemed probable that further antisyphilitic treatment would make the cure complete.

It seems certain that in this case one was dealing with meningovascular syphilis with vascular narrowing (or occlusion) in the domain of the system of the sulcocommissural arteries distal to the branches that supply the commissure, Clarke's columns and the bases of the posterior horns. In this connection the diagram of the arterial supply of the spinal cord accompanying Stähli's article is worthy of careful study. When more proximal arteries are thrombosed, complete recovery can scarcely be expected.

When an acute anterior poliomyelopathic syndrome appears in a patient who has syphilis, it would seem wise, therefore, to institute intensive antisyphilitic treatment promptly on the chance that changes in the cord that are not already irreparable may be prevented from becoming so by restitution of better circulatory conditions in the cord through regression of the vascular syphilitic process.

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ARTERIAL HYPERTENSION FOLLOWING METRAZOL SHOCK THERAPY

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Shock therapy has become one of the most widely used treatments in psychiatric practice. No report could be found in the literature of the initiation of hypertension following the use of metrazol shock therapy. In the following case hypertension developed during a course of metrazol shock treatments and has persisted over the four years since the treatment.

REPORT OF A CASE

A woman aged 47, with a negative family history for hypertension, had married when 26 years of age and had given birth to two children, now aged 18 and 15, who are healthy. She had a "nervous breakdown" at the age of 28, from which she recovered without hospitalization, and made a satisfactory and happy adjustment until her present illness. Her husband's death in 1934 was a severe blow to her. Because of metrorrhagia artificial menopause was produced by roentgen therapy in January 1936. After this she appeared less well physically to her friends and family, but made no specific complaints. In November 1936 she manifested her first mental symptoms, in the form of somatic delusions. She became depressed and self depreciatory and expressed the belief that her heart had stopped beating and that her organs had disintegrated. She was admitted to a general hospital just before Christmas 1936, but showed no improvement; she was transferred to the Menninger Psychiatric Hospital in June 1937.

Here she failed to respond to milieu therapy but continued to have delusions and at times required tube feeding. After hearing reports of beneficial results with metrazol shock therapy for depressions (my associates and I first used it for schizophrenia in October 1937), we decided to employ it in this case. The original physical examination had revealed only that the patient had had a previous amputation of the breast (in 1935) and was 20 pounds (9.1 Kg.) underweight. The results of laboratory examination were normal. The blood pressure, measured repeatedly over several months, ranged from 100 to 122 mm. systolic and 74 to 88 mm. diastolic.

The first metrazol treatment was given on May 3, 1938; the blood pressure before the treatment was 110 systolic and 80 diastolic, and five minutes after the treatment it was 130 systolic and 90 diastolic. In the second treatment, on May 10, the pretreatment pressure was 120 systolic and 80 diastolic and the post-treatment pressure was 150 systolic and 100 diastolic. On the fourth treatment, on May 17, the pretreatment pressure was 160 systolic and 110 diastolic, and the post-treatment pressure was 180 systolic and 100 diastolic. On the fifth treatment, on May 24, the initial pressure was 140 systolic and 100 diastolic and the pressure after the treatment was 170 systolic and 100 diastolic. On the seventh treatment,

From the Menninger Psychiatric Hospital.

on May 27, the initial pressure was 164 systolic and 100 diastolic and the post-treatment pressure was 200 systolic and 110 diastolic. Because it was observed that the blood pressure remained elevated and the seven treatments had produced no improvement in the mental picture, the metrazol therapy was stopped.

The shock therapy did not change the patient's mental state. She dreaded each treatment and on every occasion manifested great anxiety prior to the session. However, she responded some twelve months later to psychotherapeutic help, which, however, was not attempted systematically until about six months after the metrazol therapy. She improved sufficiently to leave the hospital in February 1941 (three and a half years after admission), and since that time she has reestablished her home, social and community activities and has been fairly well, both physically and mentally. The significant change following the metrazol therapy was the increased blood pressure, which has remained consistently between 175 and 190 systolic and 115 and 125 diastolic. There has been no physical complaint, and physical and laboratory studies have revealed nothing abnormal.

COMMENT

Although a careful search has been made of the literature, the complication or association of hypertension with metrazol therapy apparently has not been recorded. It is well recognized that the blood pressure usually increases at the time of the convulsion, just as it did in this case, and that the anxiety manifested prior to the treatment often gives rise to considerable increase in blood pressure. A survey of 100 cases in which we employed treatment with metrazol similar to that in this case (before we began the use of curare and electroshock therapy) showed the following figures for maximum blood pressure occurring during the course of a series of treatments:

Mm. Systolic	No. of Cases
No rise over 140	17
140 to 149	6
150 to 159	15
160 to 169	13
170 to 179	8
180 to 189	17
190 to 199	6
200 to 209	5
Over 210 (the highest 220)	3
Fall from pretreatment to post-treatment pressure	10

In the last group of cases those in which there was a fall from the pretreatment to the post-treatment pressure, the decrease is probably explained on the basis of the anxiety and apprehension manifested in anticipation of the treatment.

The mechanism of the cardiovascular dynamics or the psychodynamics in this case is not clear. One might speculate that the anxiety and fear connected with the treatments were as important in producing

the hypertension as was the drug or the convulsions. The clinical psychiatric picture did not change at the time, either as a result of the treatments or with the development of the hypertension, but later it did. The psychologic state, as shown by the delusions both before and after the metrazol treatment, was nihilistic: The patient said that she had no stomach, no lungs, only "what remained of a brain," etc. She pleaded to "be done away with" though she never made any suicidal attempts. The unconscious psychologic state, as represented by her hypertension, remains self destructive, even to the present time. Many psychotherapeutic sessions, continued up to the present, have disclosed a continued technic of self defeatism, great activity and effort, with at times poor efficiency, and many dreams in which through some action on her own part she is acutely threatened. Even without an explanation of the cause of the hypertension, this case seemed of sufficient importance to be reported.

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Technical and Occasional Notes

AN APPARATUS TO BE USED IN RECORDING TREMORS

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In the present report an efficient and flexible method for recording tremor is described. Numerous ways of obtaining graphs with a Marey tambour, or related apparatus, have been devised, of which that used by de Jong [1] is one of the most recent and best.

The method reported here utilizes a rubber diaphragm over the rim of an ordinary "balanced armature" loud speaker. The cone has been sealed with multiple layers of collodion and the rubber diaphragm cemented with rubber cement to assure air tightness within the chamber. With the tremulous hand placed on the diaphragm, motion is transmitted mechanically and produces variation in the reluctance of the magnetic path, which thus sets up in the alternating current coils a varying electromotive force. This, in turn, is amplified and recorded by the electromagnetically operated ink-writing pens of a Grass electroencephalograph.[2] The paper can be run at different speeds, 3 cm. per second being the rate most often used in this clinic.

This particular unit is designed to vibrate the movable aluminum button in the throat of the cone. A short soft iron bar, armature or reed is pivoted at its center, so that its ends are free to swing back and forth like a seesaw about this pivot. Each end of the armature moves between two pole pieces of the permanent polarizing magnet, and these are arranged with the relative magnetic polarity shown in figure 1. Around the armature is a stationary coil consisting of several thousand turns of fine wire, through which the current is sent. Enough clearance is provided between the armature and the inside of the coil so the motion of the armature is not restricted by the coils.

The balanced armature unit has a high degree of perfection and will give good performance if it is operated properly, with some regard for its limitations. One of its serious limitations is that for good sensitivity the air gap between the armature and the pole pieces must be made very small in order to reduce the reluctance of the magnetic circuit and to obtain a strong magnetic field. If the air gap is made large in order to provide for greater amplitude of vibration, the strength of the field decreases, with a proportionate loss in sensitivity. However, this presents no

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1. de Jong, H., and Schaltenbrand, G.: Deutsche Ztschr. f. Nervenh. **86**:129, 1925; Neurotherapie **7**:1, 1925. These investigators described the use of an ordinary muscle pelote attached to the recording muscle by a wide leather band. A tube with a fitting piece connected the pelote to a Marey tambour. The lever of the tambour was so arranged as barely to touch the surface of the smoked drum.

2. The amplifiers were built by Mr. A. M. Grass, 100 North Bayfield Road, Quincy. Mass.

serious problem, for the frequency of the Grass electroencephalograph is limited to approximately 75 to 100 per second.

The mechanism of action is shown in figure 1, and samples of records obtained from patients are given in figure 2 *A* and *B*.

APPLICATION OF APPARATUS

This apparatus is most valuable in recording fine tremors. The Grass apparatus is easily capable of measuring a frequency of 75 per

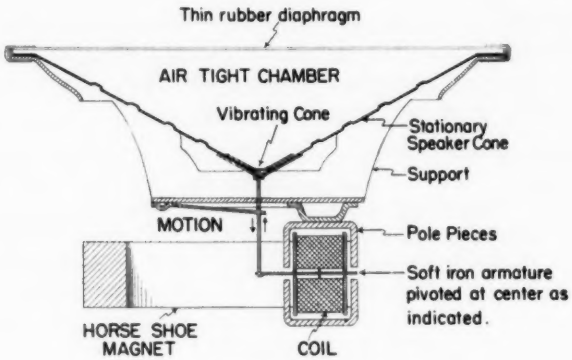

Fig. 1.—Cross section of the unit.

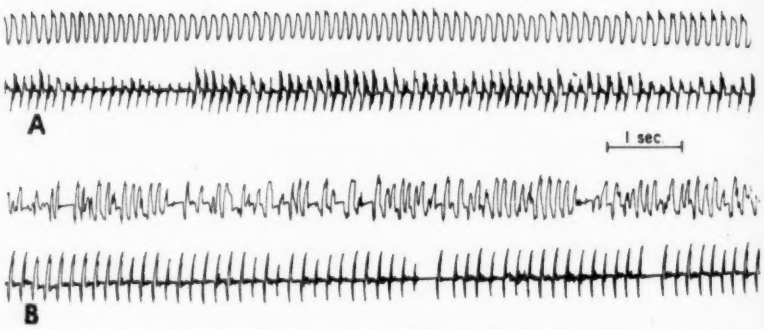

Fig. 2.—*A*, recordings of the tremor in a case of paralysis agitans (top) and the diadokokinesis (tapping) of the same hand (below). Note the regular, 7 to 8 per second tremor, with tapping at 7 to 8 per second.

B, recordings, showing the hysterical tremor of the hand (top) and the diadokokinesis of the same hand. Compare with *A*. Note the grossly irregular tremor, with several runs of waves at 8 to 10 per second, and the tapping, which is distinctly slower than the faster rates of tremor.

second, which is at least three times as fast as is necessary in clinical work. It is a simple matter to attenuate the excursion of the recording needles to differentiate tremor from variations in the position of the hand and fingers.

The apparatus is particularly valuable in measuring the irregularities in the total picture, including waxing and waning of the tremor, both fine and coarse.

The apparatus is flexible, for it can be used in any plane. Horizontal tremors of the hand are especially easy to evaluate, both as to frequency and as to irregularity in form of the oscillations, as well as to disappearance of tremor under various situations. The apparatus is small enough to hold in the hands, if desired, which permits the examiner to adapt to unusual positions or even to follow slowly moving parts, such as the head in cases of torticollis.

The apparatus is simple to use with the electroencephalographic apparatus. It does not cause outside static electricity sufficient to interfere with the simultaneous recording of electromyograms.

It has three limitations: (1) Coarse, irregular movements, such as those of athetosis or chorea, cannot be evaluated; (2) there can be no differentiation of asymmetric finger movements which bring different fingers down successively in a series of contacts with the diaphragm, unless the error is specifically guarded against by getting records from single fingers individually, and (3) the relationships of the moving parts, that is, the total pattern, cannot be adequately approximated.

In spite of its limitations, the apparatus records characteristics, especially frequency, which might prove useful in seeking the origin of tremor, such as striatal or other localized lesions or diffuse metabolic, infectious or psychogenic processes.

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

PREGANGLIONIC COMPONENTS OF THE FIRST THORACIC NERVE: THEIR ROLE IN THE SYMPATHETIC INNERVATION OF THE UPPER EXTREMITY. ALBERT KUNTZ and JOHN B. DILLON, Arch. Surg. **44**:772 (April) 1942.

In cats and rhesus monkeys the volume pulse wave in the toe or the finger pads was recorded by means of the photoelectric plethysmograph, while an afferent stimulus (ice or faradic stimulation) was applied to one of the lower extremities. Records were taken before operation, after extirpation of the second and third thoracic segments of the sympathetic trunk and after the additional extirpation of the cervicothoracic ganglion. Reflex vasoconstriction was elicited after section of all preganglionic fibers below the first thoracic nerve which are involved in the sympathetic innervation of the upper extremity. Preganglionic components of the first thoracic nerve must, therefore, effect synaptic connections with sympathetic ganglion cells the axons of which extend into the upper extremity. After extirpation of the cervicothoracic ganglion as well, only occasional slight vasoconstriction was elicited from some of the digits. This is explained on the assumption that these efferent impulses were conducted by sympathetic fibers which arise below the third thoracic segment, ascend in the vertebral canal and join the lower cervical and first thoracic nerves. If the conditions in man are comparable to those in the monkey, it is evident that complete sympathetic denervation of the upper extremity cannot be accomplished by any operative procedure which leaves the cervicothoracic ganglion with its gray communicating rami intact and does not interrupt the preganglionic components of the first thoracic nerve.

RASMUSSEN, Montreal, Canada.

SYMPATHETIC DENERVATION OF THE FEET AND LEGS OCCURRING SPONTANEOUSLY OR AS A RESULT OF DISEASE. HARRIS B. SHUMACKER JR., Bull. Johns Hopkins Hosp. **71**:1 (July) 1942.

Shumacker studied the effects of denervation on 5 patients, using the following criteria: (1) stability of cutaneous temperature on exposure to cold and inability to influence the cutaneous temperature by such tests as body heating and procaine block of the peripheral nerves; (2) absence of sweating as shown with the Minor test; (3) occurrence of extremely high cutaneous resistance under conditions which favor the lowest possible cutaneous resistance, such as heating the entire body in a heating cabinet until general sweating is profuse.

Both sweating and high cutaneous resistance under the conditions of the test were not found to be absent except when the sympathetic innervation had been interrupted by anesthesia, operation or disease. All 5 patients showed complete loss of sympathetic innervation to various portions of the feet and legs, occurring either spontaneously or as a result of their disease. No correlation was noted between the areas of hypalgesia and the sharply delimited areas of loss of sympathetic innervation, and there was no rigid relation between the degree of vasomotor disturbance and the loss of sensation or muscular power.

The circulation in the feet of some of the patients appeared to be better than the state of calcification and the occlusion of major arteries would have led one to expect. This naturally occurring sympathetic loss should help in the same manner

as does sympathectomy in those cases of occlusive disease with a significant element of vasospasm, if there are sufficient patent blood vessels in the vascular bed to permit an adequate circulation when they are kept in maximal vasodilatation.

PRICE, Philadelphia.

THE BLOOD LACTATE-PYRUVATE RELATION AND ITS USE IN EXPERIMENTAL THIAMINE DEFICIENCY IN PIGEONS. E. STOTZ and O. A. BESSEY, J. Biol. Chem. **143**:625, 1942.

It has been found that in a variety of conditions, such as excitement, exercise, anoxia and different degrees of fasting, considerable fluctuation in the pyruvic and lactic acid contents of the blood may occur. Nevertheless, a strict relation between the two is maintained, so that a normal relation can be expressed graphically or by formula. This was found true in human beings, rats and pigeons. Thus, although the actual level of pyruvate or lactate individually can serve as a measure of the aforementioned factors, and under carefully controlled conditions may even reflect true changes in the metabolism of either component, only a deviation in the normal relation between the two components is rigorous proof of a more fundamental disturbance. Therefore the use of this relation eliminates the otherwise difficult decision as to whether a given increase in pyruvate is due to genuine disturbance of pyruvate metabolism or to changes in difficultly controlled experimental conditions. Such a change in the lactate-pyruvate relation of the blood has been noted in pigeons during the course of acute and chronic thiamine deficiency, indicating a pronounced decrease in pyruvate breakdown. The use of this relation has, in fact, made it possible to note a disturbance of pyruvate metabolism early in the course of acute thiamine deficiency and to distinguish with assurance between relatively small degrees of chronic thiamine deficiency in pigeons. Since the colorimetric determination of lactic acid is so simple, even as compared with the pyruvate estimation, it is suggested that both the lactate and the pyruvate level be considered, rather than the pyruvate alone, to determine fundamental changes in pyruvate metabolism.

PAGE, Indianapolis.

THE EFFECT OF CORTICAL DESTRUCTION UPON RESPONSES TO TONES. L. A. PENNINGTON, J. Comp. Neurol. **74**:169 (Feb.) 1941.

Pennington studied the effects of restricted bilateral lesions within the auditory areas of the rat's cerebrum on (1) the animal's already acquired level of adaptive performance to a 1,000 cycle tone and (2) the acquisition of adaptive responses to the same tonal stimulus in the untrained animal. Forty-two male albino rats were divided into three groups. In the first group each animal was operated on after the acquisition of the adaptive response to tone. After seven days the animals were retrained to the original stimulus. Seventeen days later some of them were given a second, postoperative retention test. The animals in the second group were trained initially thirty days after bilateral cortical operations in and near the auditory areas had been performed. The animals in the third group served as controls. They were trained and tested in a manner identical with those in the two experimental groups except that no cortical operations were performed. After the completion of the postoperative retention tests the animals were killed and the brains examined microscopically to determine the extent of the lesions. As a result of the study a subordinate region within the auditory cortex was delimited. Analyses of the postoperative retention scores indicated that partially complete bilateral destruction of the subordinate area alone results in reduced efficiency in the auditory problem box. Retention of the adaptive act after postoperative retraining was equivalent to the retention of normal animals. This was evinced by the marked degrees of retardation in initial learning in the case of the animals operated on.

FRASER, Philadelphia.

THE SIGNIFICANCE OF AN ABNORMAL ELECTROENCEPHALOGRAM. DENIS WILLIAMS, J. Neurol. & Psychiat. **4**:257 (July-Oct.) 1941.

Williams studied 901 subjects to determine the relative significance of an abnormal electroencephalogram in groups of normal subjects and in persons with abnormal states. The electroencephalograms were taken both at rest and after overbreathing. The norm and its deviations were evaluated according to certain criteria of abnormality, which did not differ essentially from those of other investigators. In the normal groups, abnormalities varied from 5 per cent, in highly selected normal subjects (R. A. F. personnel), to 10 per cent, in less carefully selected normal subjects from the army personnel. Abnormal electroencephalograms were present in 26 per cent of a group of psychoneurotic patients, indicating a more frequent constitutional abnormality in such persons than in normal subjects. The percentage abnormality in patients with epilepsy ranged from 55, in subjects with grand mal, to 90, in patients with more than one type of fit. Forty per cent of epileptic patients had a normal electroencephalogram between seizures. According to the author, the abnormalities seen in the electroencephalograms warrant a nonspecific diagnosis of epilepsy, but the recognition of the specific type must be based on clinical observations. In post-traumatic conditions the percentage abnormality varied from 40, in chronic states, to 58, in the more acute states. Seventy-five per cent of the subjects with an abnormal response to hyperventilation showed abnormalities in the resting encephalograms. The author arrives at the following conclusions: 1. An abnormal electroencephalogram in an otherwise normal subject is evidence of an inborn constitutional abnormality involving the central nervous system. 2. This abnormality appears to be nonspecific and may manifest itself in the subject or his offspring as a behavior disturbance, which may be psychoneurotic, psychopathic, psychotic or epileptic.

N. MALAMUD, Ann Arbor, Mich.

THE FUNCTIONS OF THE CEREBELLUM. L. ECTORS, Confinia neurol. **4**:181, 1942.

Ectors states that the cerebellum functions as a retarding center to which the various motor systems are subordinated. Smooth and striated muscles and tonic and dynamic contractions are under its influence. In every muscular contraction or tonic reaction an impulse is directed toward the cerebellum, and a retarding impulse is returned. This tends to brake the lengthening and shortening of the muscles.

The peculiar histologic character and the uniform structure of the cerebellum can be explained only by a uniform and independent function. The absence of retardation shows itself in the clinical syndrome and in observations on animals in which the cerebellum has been removed. Ectors states that it is possible to construct three main reflex arcs. These are the keys to the various motor reflexes, and their connections occur at the respective motor centers on which cerebellar retardation is exerted. His results are based on known facts and on results of experiments on man and animals with injury to the cerebellum. Extirpation in the Macacus monkey produces an increase in the amplitude of the vestibular reflexes. In the cat and pigeon extirpation does not abolish the static reflex.

DEJONG, Ann Arbor, Mich.

THE VALUE OF BROMIDE DETERMINATIONS IN THE DIAGNOSIS AND TREATMENT OF BROMIDE INTOXICATION. M. G. GRAY and MERRILL MOORE, Confinia neurol. **4**:213, 1942.

Gray and Moore state that the determination of the bromide concentration in the blood has become common as an aid in the diagnosis and treatment of patients with mental disease. There is an individual variation in the capacity to excrete bromides, however, and this and other factors, including the chloride intake and excretion, the dietary intake and the water balance, are all of importance in bromide intoxication. These factors have been overlooked by most investigators.

The bromide level of the blood at which toxic symptoms appear and the extent of chloride replacement vary. Cases have been reported in which persons with an extremely high bromide content of the blood showed no toxic symptoms and others in which bromide intoxication was demonstrated while the bromide level was low. Determination of the blood bromides is valuable when carried out accurately, but because of extreme individual variations it is useless to attempt to correlate the symptoms with absolute bromide levels. Comparison of the chloride and the bromide levels in the blood and urine is more valuable than isolated determinations of the blood bromides, but all laboratory data should be used only as presumptive evidence, the clinical condition of the patient being the more important diagnostic and therapeutic index.

DEJONG, Ann Arbor, Mich.

NITROGEN BALANCE IN PATIENTS SUFFERING FROM MELANCHOLIA. H. I. SCHOU and C. TROLLE, Acta psychiat. et neurol. **16**:243, 1941.

Schou and Trolle examined 16 patients with melancholia, 15 of whom were women and 1 a man. All were classified as manic depressive. In 14 of the 16 cases a nitrogen retention of 0.5 to 1.5 Gm. of nitrogen in twenty-four hours was found. During metrazol treatment this retention was further increased. After recovery, either through metrazol treatment or spontaneously, the nitrogen excretion was at the same level as the nitrogen intake. The 2 remaining patients had an increased nitrogen excretion during their melancholia. After recovery the nitrogen excretion equaled the nitrogen intake. The authors conclude that melancholia is apparently associated with abnormal nitrogen metabolism, since in none of their 16 patients were the nitrogen intake and the nitrogen excretion at the same level. These findings were constant in the patients at several examinations, and at no time did a patient change from one type to another.

ADLER, Boston.

THE BEHAVIOR OF MOTOR UNITS IN HEALTHY AND IN PARETIC MUSCLES IN MAN. H. SEYFFARTH, Acta psychiat. et neurol. **16**:261, 1941.

Seyffarth found that as fatigue develops in voluntary muscular effort there is a gradual decline in the frequency of discharge of individual motor units in the muscle. This indicates that fatigue is accompanied by progressive inhibition (slowing) of discharge from the anterior horn cells, due either to "primary" fatigue of the cells or to the inhibiting effect of afferent impulses from the acting muscles. Since occlusion of the blood supply of the limb or direct pressure on the mixed nerve to the muscle greatly enhances this decrease in frequency of discharge, the author concludes that the inhibiting effect of afferent impulses from the acting muscles is the more important causal factor.

Seyffarth found that the electrical changes accompanying fatigue are the same in paretic muscles (old poliomyelitis; traumatic palsy) as in normal ones.

BRENNER, Boston.

Psychiatry and Psychopathology

THE ORIGIN AND DEVELOPMENT OF NERVOUS DISTURBANCES EXPERIMENTALLY PRODUCED. W. HORSLEY GANTT, Am. J. Psychiat. **98**:475 (Jan.) 1942.

Gantt extended study of the original pavlovian experimental neuroses along three main lines: the production of a chronic anxiety-like neurosis, the early detection of the breakdown by measurements of autonomic function, with the animal under artificial strain, and study of such a state of imbalance, together with the involvement of physiologic systems. He used a classic pavlovian method for inducing conditioned reflexes in animals and then, by the interjection of a

difficult situation based on a strong excitation, induced a conflict. In an acute conflict, the dog showed variations in his general behavior, loss of equilibrium between all the conditioned reflexes and, finally, variations in heart rate and respiration. An incipient nervous imbalance could be detected by measuring the departure from normal in certain autonomic responses. Development of a permanent disturbance under strain tends, at least in part, to have effects on the stability of the animal, for of 3 animals subjected to identical situations of conflict, in 1 a chronic neurosis developed for a period of nine years. Throughout this time the former food signal produced the response of an ordinary dog to actual pain. Any new elements brought into the old environment became capable of producing this response. When exposed to the environment or to the specific stimuli, this animal manifested inhibition of salivary secretion, a respiratory tic or other changes in respiration, tachycardia, intractable pollakiuria and decrease in the time required for sexual reflexes, such as erection and ejaculation. Normal sexual relations have a temporary dissipating effect on the neurosis. The twenty-four hour activity of neurotic animals does not differ from that of the normal. The dog with chronic neurosis was rested for eighteen months in the laboratory, with no effect on the neurosis. He was then transferred to the country for two months, where he showed considerable improvement, but on his being returned to the laboratory, the symptoms gradually reappeared.

FORSTER, Boston.

ELECTROENCEPHALOGRAPHIC STUDIES IN DELINQUENT BEHAVIOR PROBLEM CHILDREN. NORMAL Q. BRILL, HERTA SEIDEMANN, HELEN MONTAGUE and BEN H. BALSER, Am. J. Psychiat. **98**:494 (Jan.) 1942.

Brill, Seidemann, Montague and Balser made electroencephalographic studies on 28 children with delinquency behavior problems, who varied in age from 7 to 15 years. Two of the children with sexual offenses but no other behavior disorder had normal electroencephalographic tracings. Three children were neglected, and they likewise had no electroencephalographic disorders. Six children were classified as having behavior disorders associated with known or suspected disease of the brain or epilepsy. Of these, all but 1 had abnormal cortical potentials. Six children had behavior disorders with pronounced neurotic or psychotic features, and 4 of these had abnormal electroencephalographic tracings. The remaining 11 children suffered from behavior disorders unassociated with overt organic or functional disorders, and 8 of these had abnormal electroencephalograms.

In view of the high incidence of electroencephalographic abnormalities associated with such behavior disorders (61 per cent of 28 cases), the authors suggest the presence of an underlying cerebral disorder in the majority of children presenting severe behavior problems.

FORSTER, Boston.

DELINQUENCY AND THE ELECTROENCEPHALOGRAPH. WARREN T. BROWN and CHARLES I. SOLOMON, Am. J. Psychiat. **98**:499 (Jan.) 1942.

Brown and Solomon made electroencephalographic studies on 20 boys committed to a state training school for delinquency. Only 3 of the 20 boys had normal cortical potentials. Eleven had slow, square-topped waves, similar to those seen with psychomotor epilepsy. Three patients presented a subclinical petit mal type of activity, while the remaining 3 showed abnormal cortical potentials not characteristic of either the petit mal or the psychomotor type of disturbance. All patients with severe or moderate degrees of delinquency showed abnormalities of the electroencephalogram. Seven patients with conspicuous behavior difficulties had grossly abnormal electroencephalograms of the psychomotor type and were placed under treatment with dilantin. The results of this therapy are encouraging to date.

FORSTER, Boston.

ALCOHOLISM AND MENTAL DISORDER IN MASSACHUSETTS, 1917-1933. NEIL A. DAYTON, MERRILL MOORE, DOROTHY A. KUNBERGER and M. GENEVA GRAY, Quart. J. Stud. on Alcohol **3**:50, 1942.

In this study of 56,579 first admissions to mental disease hospitals in Massachusetts, it was found that chronic alcoholism was a prominent factor in about one fifth of the total number. The high point for admissions due to this factor was 1917, and never again during the era of national prohibition did its incidence become as high. In both males and females, chronic alcoholism was most prevalent between the ages of 40 and 49. Single marital status, education, rural habitat, comfortable economic status and native-born parents were all factors associated with a minimal occurrence of alcoholism in this group of patients.

DRAYER, Philadelphia.

ACCULTURATION PROCESSES AND PERSONALITY CHANGES AS INDICATED BY THE RORSCHACH TECHNIQUE. A. I. HALLOWELL, Rorschach Research Exchange **6**:42 (April) 1942.

Hallowell wished to test the thesis that if there is close connection between the organization of personality and culture patterns, changes in culture should produce changes in personality. The Rorschach technic was used to test exactly to what extent this method, combined with other means of observation, could be used in the study of personality and culture.

The subjects were two groups of Indians; the Lakeside Indians, consisting of 35 men and 23 women, and the Inland Indians, consisting of 30 men and 13 women. In addition, 49 children of both groups were studied. The Inland group was by far the least accultured and still clung to many native habits. The Lakeside Indians were the most accultured and had discarded all native customs. The latter group had had the most contact with white men and their ways of living, although the Inlanders also had had some contact.

From the test, it was found that the Inland Indians had pronounced "introversive" tendencies. They were long in answering; their answers were cautious and deliberate; they appeared to be inhibited and showed a fear of self expression. The Lakeside Indians, on the other hand, answered with great speed, which almost averaged that of the white man, and appeared less inhibited. Among the children, however, even the Inlanders nearly approached the speed of white men in answering.

The Inland men were found to be the most introversive, and their women were only less so by a small degree. In the Lakeside group, the men were also the more introverted of the two sexes. Their women had been most affected by contact with white men through intermarriage and had gone far in assuming the habits of the white people.

Personal and social adjustments showed that the women were by far the better adjusted, particularly in the Lakeside group.

MARCOVITZ, Philadelphia.

THE RELATION BETWEEN BLOT AND CONCEPT IN GRAPHIC RORSCHACH RESPONSES. KATE N. LEVINE and JOSEPH R. GRASSI, Rorschach Research Exchange **6**:71 (April) 1942.

In the graphic Rorschach technic the subject is permitted to present his own drawing of what he sees in each Rorschach blot.

One hundred and fifty subjects were tested and 1,700 drawings were obtained. The presentations varied from exact copies of the blots ("blot-dominated" responses) to drawings which contained none of the outstanding blot elements ("concept-dominated" responses). The former type of drawing always showed a clear picture of the blot and could be recognized easily, but the concept-object was rarely obvious. The latter type of response showed a clear picture of the object, but the blot to which it referred was hard to determine.

On analysis, the subjects who used the "blot-dominated" responses were patients with dementia paralytica, cerebral injury, arteriosclerosis, alcoholism with

encephalopathy and convulsive disorders with demonstrable organic pathology. Deteriorated schizophrenic patients, some depressive patients and some mentally defective persons used this interpretation also, but to a lesser degree. No normal subjects used it. The author explains that the group using this interpretation to the larger degree had lost the ability to abstract and had reacted to the immediate situation presented. The group using this interpretation to a lesser degree did so not from compulsion but from lack of a clear independent concept.

The graphic Rorschach method has made it possible to understand better the responses of the disturbed mental function. MARCOVITZ, Philadelphia.

PSYCHIATRIC PROBLEMS IN MILITARY AVIATION. R. BARRY BIGELOW, War Med. **2**:381 (March) 1942.

Psychologic difficulties are the most common cause of flying problems. They commonly cause breakdowns before the flier has had 200 flying hours. Bigelow reviews these difficulties in three situations: the methods of selection of pilots; the difficulties arising during the training period, and the problems arising in active service.

There are no adequate criteria yet known whereby the selection of pilots can be made with any exactness. Those who become successful pilots seem to have three characteristics: (1) a strong desire to fly; (2) a college education, and (3) good judgment. Those who fail as pilots seem to have the following characteristics: (1) an indifferent attitude toward flying; (2) a grade school education, and (3) evidence of emotional instability in their history.

The author advises that in the present state of knowledge, it is important that the applicant's examination include (1) a questionnaire on his life history, (2) the Wonderlic modification of the Otis intelligence test, (3) a personal interview with a psychiatrist, (4) some psychomotor coordination test and (5) the Rorschach test.

Among 1,200 to 1,800 students in training, the following causes of inefficiency were found:

Diagnosis	Student Pilots Referred for Neuropsychiatric Consultation, January to June 1940	Student Pilots Appearing Before the Advisory Board, January to June 1940
Schizophrenia	2	0
Mild depression	2	0
Anxiety state	1	1
Paranoid trend	0	4
Conversion hysteria		
Predominantly sensory	0	3
Predominantly motor	2	2
Predominantly visceral	2	0
Hypochondriasis	0	1
Phobia	3	1
Obsessive thinking	0	1
Psychopathic personality	0	1
Constitutional inadequacy	1	2
Fear reaction to flying	8	8
Fear of failure seriously interfering with performance	0	24
No psychiatric diagnosis	3	46
	24	94

If there was a previous clearcut history of an actual neurosis or psychosis or of a definite trend in that direction, the candidate was usually pronounced unsuitable. Applicants who were borderline and showed a schizoid psychopathy, a mild reactive depression, a tendency to be irritable and to project their difficulties under discipline or criticism, tenseness and anxiousness, conversion symptoms and excessive, but easily relieved, fatigue had to be judged as to flying ability on their individual symptom pictures.

Pilots and ground crews on active service showed much fewer psychologic difficulties than students because they had lost their fear of flying and had no fear of not becoming successful fliers—two difficulties that occurred rather commonly among the student fliers. Their psychologic difficulties were as follows:

Diagnosis	Flying Personnel	Others
Mild depression	1	0
Anxiety state	1	2
Hysteria		
Predominantly psychic	0	2
Predominantly sensory	0	2
Predominantly motor	0	0
Compulsion neurosis	1	0
Psychopathic personality	0	7
Constitutional inferiority	0	3
No psychiatric diagnosis	2	1
	5	17

PEARSON, Philadelphia.

Diseases of the Spinal Cord

SPINAL EXTRADURAL CYSTS. FRANK H. MAYFIELD and EVERETT G. GRANTHAM, Surgery **11**:589, 1942.

Mayfield and Grantham add 2 cases of extradural spinal cyst to the 14 already reported in the literature. They suggest that the condition may be more common than the small number of reported cases indicates. The symptoms may resemble those of multiple sclerosis closely, and hence in some cases operation may never be performed.

The cyst in 1 of the cases communicated through its pedicle with the subarachnoid space. It was emptied and filled several times at operation before it was removed in order to demonstrate the communication clearly. The authors suggest that such intermittent changes in volume may account for the remission of symptoms often observed in cases of this lesion. Their case supports the hypothesis that extradural cysts arise from herniations of the arachnoid through defects in the dura. The symptoms followed an injury initially, and the authors point out that the dural defect may be traumatic in origin. The second case was notable because of a history of four remissions of symptoms.

In most of the cases described symptoms developed in adolescence. Paraplegia appearing at this time of life should be followed by careful search for evidences of tumor of the spinal cord even though sensory disturbances and pain may be minimal or absent.

DRAYER, Philadelphia.

SYMPTOMATOLOGY AND PATHOLOGY OF SPINAL ARACHNOIDITIS. ADOLF JUBA, Deutsche Ztschr. f. Nervenh. **152**:37, 1941.

Juba describes 2 cases of spinal arachnoiditis in men aged 57 and 50 respectively. The first patient died four days after operation and the second shortly after operation. Histologic examination revealed chronic proliferative changes in

the meninges, causing obliteration of the subarachnoid space. The spinal cord showed myelin degeneration and disease of the vessels. The author assumes that in the first case the disease developed on a syphilitic basis, since the serologic reactions were positive for syphilis. In the second case the pathologic picture in the spinal cord was classified as subacute necrotic myelitis. Spinal arachnoiditis is considered a syndrome which may be caused by various agents. Operation is indicated when there is evidence of compression of the cord, but the results are dubious. When the disease has progressed to the spinal cord, which seems to occur sooner or later in all cases observed, operation cannot be expected to bring relief. The author advises energetic treatment of the underlying disease whenever possible.

ADLER, Boston.

PATHOLOGY AND PATHOGENESIS OF LANDRY'S PARALYSIS. W. DANSMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:373 (Sept.) 1940.

Dansmann reports 15 cases of Landry's paralysis, 10 with recovery and 5 ending fatally. The author feels justified in including the 10 cases of recovery in spite of the fact that dysphagia was present in only 1. He believes these cases are instances of a milder form of the disease, without involvement of the bulb. In 2 of the fatal cases signs of bulbar disturbance did not appear until three weeks after the onset of the illness. The course of the disease in the cases of the benign form, the absence of febrile reactions and the character of the changes in the spinal fluid favor the inclusion of these cases with those of the more typical Landry's paralysis with a fatal outcome.

All the patients were adults, the youngest being 24 and the oldest 63. There were only 3 women in the series. Only 6 patients gave a history of infection of the upper respiratory tract before onset of the disease. Most of the patients had an acute course, the maximum intensity of the illness coming on not later than a week from the time of onset. In 2 patients, as already noted, the bulbar symptoms appeared after an apparently stationary course of three weeks. The clinical picture was predominantly that of lower motor neuron paralysis. There were, however, some sensory changes in almost every case, often limited to paresthesias and pain. Striking objective sensory changes were absent. In most instances the sensory changes were segmental. No definite level lesion was present in any case. In 1 case the sensory changes were of a peripheral pattern (ulnar and median). The changes in the spinal fluid consisted chiefly of increased protein, with mild or no pleocytosis. There were no clinical changes pointing to cerebral involvement. In cases of the benign form there was usually complete recovery, without residuals.

The anatomic changes were often out of all proportion to the severity of the clinical picture. The disease is mainly one of the peripheral neurons, the anterior and the posterior roots being equally affected. The spinal ganglia were not severely involved. The changes in the peripheral neurons consisted of lymphocytic infiltration, with little change in the axis-cylinders. The changes in the spinal cord and brain were mild and were chiefly perivascular round cell infiltrations, usually lymphocytic. Changes were observed especially around the third ventricle and in the region of the nuclei of the cranial nerves. Changes in the ganglion cells were minimal. In almost all the cases there was some meningeal infiltration over the cerebral hemispheres. There was little evidence of direct spread to the brain. The anatomic changes suggested extension by the blood stream. The author found more cellular infiltration of muscle than has been reported by other investigators.

Dansmann suggests a toxic cause for the diffuse changes described. He does not favor the theory that the illness is a virus infection and offers no suggestion as to the nature of the intoxication.

SAVITSKY, New York.

Peripheral and Cranial Nerves

VITAMIN DEFICIENCIES AND LIVER CIRRHOSIS IN ALCOHOLISM. NORMAN JOLLIFFE, Quart. J. Stud. on Alcohol **1**:517 (Dec.) 1940.

Jolliffe concludes from his studies that (*a*) no alcohol addict with an estimated adequate vitamin B intake had polyneuritis, and (*b*) every alcohol addict with an estimated absolute deficiency of vitamin B for twenty-one days or more had polyneuritis. Polyneuritis may develop in an alcohol addict as early as the seventh day of estimated absolute deficiency of vitamin B. He states that "alcohol has no direct toxic action (chronic) on the peripheral nerves and that polyneuritis in the alcohol addict is due to vitamin B deficiency." He asserts that the neuropathologic and clinical identity of polyneuropathy and beriberi stands today unchallenged. There is slightly less argument in regard to etiology. While no one doubts the basic nutritional deficiency in alcoholic neuropathy and the avitaminotic nature is also recognized, there are some dissenting views with regard to the specific vitamin involved. The majority of investigators believe the basic etiologic factor is a vitamin B_1 deficiency.

Belief in direct causation of polyneuropathy by alcohol has had to be abandoned in view of the following facts: (*a*) the identity of "alcoholic" neuropathy and beriberi, (*b*) the failure of neuropathy to develop in alcoholized animals, (*c*) the failure of alcoholic neuropathy to develop in adequately nourished alcoholic persons and (*d*) experimental production by vitamin B_1–deficient diets of the characteristic symptoms in the peripheral nerves and the clinical signs of neuropathy, including the neurasthenic manifestations which, the author states, always precede the onset of peripheral neuropathy.

BRACELAND, Chicago.

SYMPTOMATIC HERPES ZOSTER. CARL MUMME, Deutsche Ztschr. f. Nervenh. **152**:67, 1941.

Mumme describes the case of a man aged 39 whose right testis had been removed because of a seminoma and in whom multiple metastases later developed in the lymph glands and abdominal organs. A paravertebral metastasis had completely destroyed the spinal ganglion of the twelfth thoracic nerve and had grown into the vertebral canal. The twelfth nerve failed to show tumor tissue at autopsy. Seven years after extirpation of the seminoma, and several years after the first metastases had appeared, extensive herpes zoster developed over the right lumbar region and the right thigh, i. e., over the eleventh dorsal to the second lumbar segments. The patient died nineteen days afterward. The spinal ganglia of the eleventh thoracic and first and second lumbar nerves showed inflammatory changes, with many plasma cells. The picture was characteristic of herpes zoster caused by a virus. In the opinion of the author, the metastases of the seminoma favored the growth of the virus and did not cause the herpes zoster.

ADLER, Boston.

A CASE OF SUBACUTE ASCENDING POLYRADICULONEURITIS WITH ALBUMINOCYTOLOGIC DISSOCIATION. T. OTT, Schweiz. Arch. f. Neurol. u. Psychiat. **48**:83, 1941.

A woman aged 49 had periarthritis of the left shoulder on first examination. She had always been in frail health and for two years had been subject to attacks of furunculosis. Some months before she had suffered from sciatic neuritis. The periarthritis subsided nine months later, but soon the furunculosis recurred and injections of autogenous vaccine, which were given for the latter condition, induced mild febrile reactions. A year after the first examination the patient began to complain of weakness in her lower extremities and of pain in the back, legs and tips of the fingers. Examination revealed a sluggish pupillary reaction to light, temporal pallor of the left optic disk, absence of the knee and ankle jerks and anesthesia of the distal type, which was present in all four extremities

but was more pronounced in the lower limbs. Deep sensibility was impaired to a greater degree than was superficial sensation. The calves and nerve trunks were tender on pressure; there was considerable ataxia, and weakness was severe in the lower extremities. The sedimentation rate of the red blood cells was greatly increased, and the spinal fluid contained 1 lymphocyte per cubic millimeter and 2.684 Gm. of total albumin per hundred cubic centimeters. Loss of power later became profound in the upper as well as in the lower limbs, and finally the cranial nerves were affected; swallowing was embarrassed, and temporal pallor of both optic disks was observed. Forty-nine days after the first appearance of weakness signs indicative of massive pulmonary involvement were noted, and two days later there was evidence of serious renal involvement. The patient died fifty-four days after the onset of her last illness.

Autopsy disclosed thrombosis of the left femoral vein, bilateral pulmonary embolism, lipoid nephrosis, chronic hypertrophic gastritis and cholelithiasis. Histologic study of the nervous system revealed degeneration without inflammatory reaction in the spinal nerve roots and the posterior ganglia. The degenerative process was especially intense in the lumbosacral roots, with predilection for nerve fibers of large caliber, the myelin sheaths being involved to a greater extent than the axis-cylinders. The peripheral nerves were not examined. Retrograde degeneration of the anterior horn cells of the lumbosacral segments of the spinal cord and ascending degeneration of Goll's tracts were also noted. The blood vessels of the spinal nerve roots, leptomeninges and spinal cord were dilated and filled with blood but showed no other alteration. The cerebral peduncles were not examined; elsewhere in the brain stem the nuclei of the cranial nerves appeared to be normal. Aside from congestion of the blood vessels, nothing remarkable was observed in the cerebral hemispheres. As congestion of the small vessels was not confined to the nervous system, it seemed attributable, at least in part, to venous stasis resulting from failure of the respiratory and circulatory systems. The view is expressed that although infection by a neurotropic virus may have prepared the terrain, the polyradiculoneuritis was primarily of toxic-infectious origin.

DANIELS, Denver.

Vegetative and Endocrine Systems

BLOOD SUGAR IN A CASE OF COMPLETE HYPOPHYSECTOMY. JAMES FINLAY HART and MORTON MAGIDAY, Arch. Int. Med. **68**:893 (Nov.) 1941.

Hart and Magiday report the case of a 33 year old man who complained of headaches and failing vision for more than two years. Examination indicated that he had a pituitary tumor, and operation was performed in two stages. The surgeons believed that they had performed a complete hypophysectomy when they removed the tumor, a meningioma. About two years later the patient was again admitted to the hospital complaining of visual failure and abdominal cramps. He gave the appearance of being prematurely aged and had a high-pitched voice and feminine distribution of hair. There were marked hyperesthesia and hyperalgesia over the entire body. The fasting blood sugar levels were 80, 45 and 34 mg. per hundred cubic centimeters on different days. The results of sugar tolerance tests were somewhat erratic, with a tendency to a delayed rise and a flat curve.

It has previously been thought that the pituitary gland is essential to life, but recent work has seemed to refute this theory. From their studies on the patient, the authors agree that the pituitary is not indispensable. They suggest that the gland functions as a mechanism to raise the blood sugar level, since its removal produces low blood sugar values without shock and a plateau type of dextrose tolerance curve.

BECK, Buffalo.

TUBERCULOMA OF HYPOPHYSIS WITH INSUFFICIENCY OF ANTERIOR LOBE. JACK D. KIRSHBAUM and HERMAN A. LEVY, Arch. Int. Med. **68**:1095 (Dec.) 1941.

Among 14,160 autopsies performed at Cook County Hospital from 1929 to 1940, Kirshbaum and Levy found only 2 cases of tuberculosis of the anterior lobe of the pituitary with symptoms of pituitary insufficiency; yet there were 652 cases of various types of pulmonary tuberculosis and 368 cases of tuberculous meningitis. Neither of the 2 cases of hypophysial tuberculoma occurred in patients with tuberculous meningitis.

In the first case, that of a woman, the criteria for the diagnosis of pituitary cachexia (Simmonds' disease) were fulfilled with amenorrhea, severe asthenia, marked and rapid loss in weight, hypotension, dryness of the skin and hair, low basal metabolic rate and high dextrose tolerance. Autopsy revealed complete destruction of the anterior lobe of the hypophysis by a tuberculous lesion. In the second case, that of a man, signs of pituitary failure, such as a eunuchoid body build with female distribution of hair and hypotension, were present. Autopsy disclosed an old sclerosed tuberculoma of the anterior lobe of the hypophysis, with effects of prolonged pressure on the optic chiasm.

The pathologic picture of tuberculosis of the hypophysis as described by Simmonds may be associated with, or secondary to, the following conditions: (1) acute miliary spread of the disease; (2) nearby meningitis or osteomyelitis of the sphenoid bones, or (3) hematogenous metastasis, with formation of large but slow-growing conglomerate tubercles. The first two types are acute, run a rapid course and generally terminate in early death; they usually do not produce local symptoms, but if local symptoms result they are overshadowed by the general picture of the causative disease. The third type, however, can produce various syndromes as a result of pressure on the pituitary gland and on the surrounding structures, similar to any expanding lesion in this area.

Tuberculosis of the hypophysis is a very infrequent manifestation of tuberculosis of the central nervous system. Pituitary cachexia is rarely due to the destructive effect of tuberculosis, since there are but 3 authenic cases on record, including the case the authors report.

BECK, Buffalo.

THE ELECTRO-ENCEPHALOGRAM IN ADDISON'S DISEASE. W. C. HOFFMAN, R. A. LEWIS and G. W. THORN, Bull. Johns Hopkins Hosp. **70**:335 (April) 1942.

Twenty-five patients with Addison's disease were studied with a Grass ink-writing, 6 channel instrument and a kymograph speed of 30 mm. per second. Sensitivity to voluntary hyperventilation was estimated by measuring the time which elapsed before large, slow waves appeared. Sensitivity to low oxygen tension was studied by administering a mixture of 12 per cent oxygen in nitrogen for ten minutes. A dry meter was used to measure the respiratory volume before, during and after the exposure. In 18 of 25 patients definite abnormalities were observed in the resting pattern of the electroencephalogram, which was characterized by the following changes: 1. The presence of oscillations that were slower than the normal alpha rhythm. These had a predilection for the frontal area of the cerebral cortex, and were relatively refractory to the usual effect of opening the eyes. The abnormalities in the resting pattern were typical but cannot be considered pathognomonic, as several other conditions are known to be associated with slowing of the general frequency. 2. Unusual sensitivity of the electroencephalogram to voluntary hyperventilation. This was observed in 15 of 22 patients with Addison's disease and occurred much earlier than in normal persons. 3. Reduction in the incidence of low voltage–high frequency activity (beta waves).

The abnormalities of the electroencephalogram during rest may progress during synthetic "hormone" therapy. Treatment with desoxycorticosterone acetate, aqueous adrenal cortex extract or intravenous infusions of dextrose failed to correct the abnormality in the resting pattern. The high cost of continuous therapy with aqueous adrenal cortex extract precluded administration for a prolonged period.

It was apparent from the study that restoration of blood pressure, plasma volume and electrolytic concentration failed to prevent the occurrence of the electroencephalographic abnormalities in the resting pattern. However, adrenal cortex extract therapy and intravenous infusion of dextrose did in some patients effect a marked reduction in the sensitivity to hyperventilation.

PRICE, Philadelphia.

Treatment, Neurosurgery

CONDITIONED REFLEX THERAPY OF ALCOHOLIC ADDICTION: V. FOLLOW-UP REPORT OF 1042 CASES. WALTER L. VOEGTLIN, FREDERICK LEMERE, WILLIAM R. BROZ and PAUL O'HOLLAREN, Am. J. M. Sc. **203**:525 (April) 1942.

Voegtlin, Lemere, Broz and O'Hollaren, in a follow-up report, present additional data on a series of 1,042 cases of alcoholism over an observation period of five and a half years. Among 827 cases, 532 cases of abstinence (58.6 per cent) and 295 cases of relapse (41.4 per cent) were found. In 170 cases in which treatment was given during the most recent six month period (the last half of 1940), the incidence of abstinence was 85.9 per cent and that of relapse was 14.1 per cent. In the original series of 1,042 cases, there were 43 deaths since treatment had been completed. At the time of the original publication of this method, in 1940, about 60 per cent of cures was expected. Of 142 cases observed from four to five and one-half years, cure was effected in 44.7 per cent, cure being defined as total abstinence of alcohol of all kinds for four years after completion of treatment.

MICHAELS, Boston.

THE TREATMENT OF CERTAIN MUSCULAR ATROPHIES WITH VITAMIN E, WITH A NOTE ON DIAGNOSIS AND THE ELECTROMYOGRAMS. H. R. VIETS, E. H. TROWBRIDGE JR. and T. E. GUNDERSEN, Am. J. M. Sc. **203**:558 (April) 1942.

Viets, Trowbridge and Gundersen selected 21 patients for treatment with vitamin E in the form of alpha tocopherol acetate, given either by mouth or subcutaneously. Eleven patients with a condition diagnosed as amyotrophic lateral sclerosis, 6 with progressive muscular atrophy and 4 with peroneal muscular atrophy of the Charcot-Marie-Tooth type were treated over a period of ten months, between April 1940 and February 1941 inclusive. The authors believe the diseases in question are syndromes, not only because of their multiple causes but in view of their symptomatic variability. Sensory symptoms of any kind associated with bulbar paralysis, progressive muscular atrophy or amyotrophic lateral sclerosis cannot be accepted, except on the basis of some coincident disease. False reports of recovery following various types of treatment are due in part to the inclusion of patients with sensory symptoms. The diagnosis is based on fibrillations as an unequivocal sign of degeneration of the anterior horn cells or, similarly, of the motor nuclei of the cranial nerves. Reports indicate no beneficial results from the use of vitamin E in cases of amyotrophic lateral sclerosis, progressive muscular atrophy or peroneal muscular atrophy. In general, the weight of the reported cases in the literature is against the value of vitamin E in treatment of the diseases under consideration.

MICHAELS, Boston.

ARTIFICIAL FEVER THERAPY OF JUVENILE NEUROSYPHILIS. J. C. NIELSEN, J. R. MARX and H. A. DICKEL, Arch. Dermat. & Syph. **45**:688 (April) 1942.

Five patients of ages from 11 to 20 years were treated by Nielsen and his associates in the Kettering hypertherm. Four of them presented a picture of dementia paralytica and 1 a tabetic picture without the typical dementia paralytica colloidal gold curve of the spinal fluid. Four of the patients were given a complete course of artificial fever. This consisted of fifty hours of treatment in ten

to eighteen sessions at a temperature of 105 to 106 F. One patient received an additional course of thirty hours about two and a half years after the first course. One patient died during the twelfth treatment. Necropsy showed the cause of death to be cerebral edema and subarachnoid hemorrhage. During fever therapy the patients received weekly intramuscular injections of bismuth subsalicylate and intravenous injections of mapharsen. The mapharsen was administered at the height of the fever. After the last fever treatment chemotherapy was continued for six weeks. After this, regular courses of arsenical and bismuth preparations were given up to the time of the report. The 4 surviving patients have been closely followed for one to three and a half years. At the time of writing the 3 patients with dementia paralytica are at home and all have shown definite improvement in both physical and mental activity. The condition of the tabetic patient after one year of improvement has remained stationary, except that the atrophy of his optic nerves has progressed to the point of blindness. The Wassermann reaction of 3 patients returned to normal immediately after therapy and that of the tabetic patient after two years. The normal reaction of 1 of the patients became positive at a later date.

J. A. M. A.

Results of Lobotomies at the Delaware State Hospital. P. E. Elfeld, Delaware State M. J. **14**:81, 1942.

After experience in 19 cases of lobotomy, Elfeld concludes that "successful results depend not so much on the type of psychoses as on the type of symptoms presented. Those patients who show evidence of agitation, depression, fear, worry, assaultiveness and paranoid reactions seem to have a much better prognosis for social adjustment."

Of the 19 patients, 10 had depressive features. The only truly postoperative death occurred in this group. Six patients returned home and adjusted at prepsychotic levels. Euphoria and lack of restraint prevented good adjustment of 2 of the remaining patients, and the third became maniacal after the operation. One woman with chronic mania was operated on only three weeks before this report, but seemed much quieter and more cooperative.

Eight patients were considered to have dementia praecox. The 4 patients with paranoid, assaultive trends showed definite improvement, while the other 4, with the simple or hebephrenic type, manifested little change in their condition.

Drayer, Philadelphia.

Successful Operation on Three Intracranial Cholesteatomas. Viktor Graser, Deutsche Ztschr. f. Nervenh. **152**:13, 1941.

Graser reports 3 cases of intracranial cholesteatoma. The first patient, aged 31, had right hemiparesis and motor aphasia, which developed suddenly and were accompanied by violent headaches. The left lateral ventricle was displaced downward in the encephalogram, but the arteriogram was not consistent with the diagnosis of glioblastoma. Operation revealed a cholesteatoma which covered the corpus callosum. The author explains the sudden onset of symptoms by disintegration of the tumor or by disturbance of circulation within the area of distribution of the anterior cerebral artery. The second patient, aged 33, had suffered from attacks of vomiting for two years, dizziness and disturbance of gait for one year and ringing in the right ear for one-half year. In addition, there had been dysphagia, headaches and disturbance of vision for two months. Ventriculography revealed hydrocephalus and compression of the fourth ventricle from behind. A cholesteatoma of the fourth ventricle was removed. Two months later, when discharged, he presented only minor signs of cerebellar disturbance. The third patient, a man aged 57, had been slowly deteriorating for many years. Examination showed paresis of the right hand, acalculia, agraphia, apraxia and finger agnosia. An extradural cholesteatoma, which had grown through the bone and displaced the parietal, temporal and occipital lobes, was removed. The postoperative course was uneventful, and the patient recovered completely.

Adler, Boston.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY AND PHILADELPHIA PSYCHOANALYTIC SOCIETY

O. Spurgeon English, M.D., *Presiding*

Joint Meeting, April 10, 1942

Relations of Psychoanalysis to Psychiatry. Dr. Le Roy M. A. Maeder.

Freud said: "Psychoanalysis stands to psychiatry more or less as histology does to anatomy."

Psychoanalysis started within medicine as an attempt to cure hysterical symptoms by psychologic means. Freud developed further the psychologic approach to hysteria begun by Charcot, Bernheim and Breuer. In this country therapeutic psychoanalysis is considered and practiced as a part of clinical medicine.

Psychoanalysis is empiric and scientific. Knowledge of psychologic facts and processes acquired during treatment is the sound basis of its formulations and application in treatment. Psychoanalysis has endeavored to refine and systematize the everyday methods used in understanding the other person's mental situation. In addition to objective observation, it uses introspective psychologic observation. Ernest Jones said that Freud succeeded in fulfilling the delphic injection, "Know thyself."

Psychoanalysis embodies a dynamic theory of personality, based on a knowledge of clinical psychologic entities and mechanisms. It includes a study of instincts; psychosexual development; ego; superego, or ego-ideal; cultural and environmental effects; mental mechanisms and dynamisms; interhuman relationships, including identification, transference and object relationship, and the structure of personality. It is an instrumentality of research into the mind in health and in disorder.

Psychoanalysis has helped psychiatry eliminate the artificial separation of mental from physical disease, of mental processes from physical processes; it has given impetus to psychosomatic medicine and has emphasized that psychologic factors, such as thoughts and ideas, can and do influence and disturb the function of organs morphologically intact, or bring about changes in them; it has helped psychiatry in its progress from a macroscopic, descriptive science to a microscopic, explanatory one; it has contributed to a better and deeper understanding of criminality, delinquency, behavior problems of children, the psychoses, culture and normalcy; it has developed a more penetrating and effective method for the understanding and treatment of the neuroses; it has, through its basic findings and concepts, penetrated and greatly influenced modern psychiatric thinking and practice.

Reactions of People to the War. Dr. Gerald H. J. Pearson.

Sometime ago the Philadelphia Psychoanalytic Society appointed a committee to collect data on the reactions of people to various phases of the war. This paper is a preliminary report of this committee.

Effect of the War on Children.—So far children show little or no reaction to the war except curiosity regarding certain environmental changes, such as blackouts.

However, in cases in which the family situation has been altered because one or the other parent is absent due to war work, the child shows behavior changes

as the result of feelings of insecurity and of guilt. The results of similar feelings have been found in the life histories of adults who were subjected to similar disturbances in the family constellation during their childhood during the first World War.

Effect of the War on Adolescents.—Adolescents who have a problem in their relationship to their families tend to regard military service as an escape from their problems.

Reactions of Younger Selectees to Military Service.—The majority of selectees feel that it is their duty to serve, although they are not enthusiastic about the causes of war. They state that their fathers are proud that they have been called up but that their mothers are sorrowful. Usually any talk about the war or radio programs dealing with the war have been banned in their homes.

Reactions of Older Selectees.—Some of the older selectees look on military service as a way of having a more interesting life.

Reactions of Patients to Critical Events in the Present War Since Its Start in 1939.—(*a*) The outstanding reaction was the marked indifference to and disregard of important international crises.

(*b*) To the attack on Pearl Harbor a number of patients responded with conscious fears lest they be injured or lose something valuable. In some cases this conscious fear was accompanied by an increase in intensity of symptoms; in others, by accentuation of their character pattern. A number of patients began to improve after the initial reaction.

(*c*) Those patients who showed a reaction to war in general and to specific crises tended to respond according to their childhood response to crises; for example, persons who had tried to solve their childhood difficulties by an isolationist policy showed a similar trend. Patients with a democratic ideology had attempted to solve their childhood problems, i. e., the Oedipus situation, by growing up, but had failed in some manner to accomplish this satisfactorily. Similarly, although they had democratic inclinations, they were unable really to put them into practice. Patients with a pro-Axis ideology had not been able to solve the Oedipus difficulties even as well as those with a democratic ideology.

(*d*) Female patients often reacted to the black-out with conscious or semi-conscious fantasies of rape.

DISCUSSION

Dr. Robert A. Matthews: For some time I have been interested in the emotional reaction of inductees and have asked each man examined how he felt about entering the Army. There have been some interesting responses. During the early days of the draft, when the country was not at war, a great many of the men expressed considerable enthusiasm about the service, and approximately 90 per cent answered the question by stating: "I think a year in the Army will do me good." This attitude appeared to be based on a desire to escape from the monotony of everyday life and, at the same time, indicated that only a relatively small number of the men were aware that their military service was probably not going to be limited to a twelve month period. When the length of service was increased to eighteen months, there was an alteration in the attitude to this extent: Many said, "It is probably a good thing for me to be in the Army, but I don't like the idea of being away from home for such a long time." Then, after Pearl Harbor there was a distinct change to a grimmer, less enthusiastic attitude, summed up in the phrase, "Well, I want to do my duty." Of course, there was considerable difference in the attitude of men coming from various social groups.

I have been impressed by the number of inductees who exhibited evidence of anxiety with some degree of autonomic imbalance. Indeed, if all such men were turned down, the percentage of rejections would mount materially.

Dr. O. Spurgeon English: I believe that the inductees have a definite feeling of cooperation; that there is not nearly so much dissatisfaction as one might expect after reading all the complaints about apathy and complacency. Many of

the men look forward to the Army as a change or relief from the monotony of their present jobs. A great many say, "If I have to go, I have to go." Some say, "Some one has to fight this war—it might as well be me." On the whole, I found few who did not actually want to go. As one got into the more intelligent groups, it was found that they were going from willingness to do their duty. It is my opinion that there is a general willingness to go to war and fight, even though the men are not under the pressure of propaganda which is being spread among the men in the fascist countries.

Ideation and Trends Encountered in Psychotherapy of Manic-Depressive Psychosis. DR. O. SPURGEON ENGLISH.

This paper deals with observations on patients who had suffered from one or more attacks of manic-depressive psychosis and who were receiving psychotherapy in the free interval. Four patients had the depressive and 2 the manic type. In some instances the psychotherapy was orthodox freudian psychoanalysis, and in others it was a psychotherapeutic interview about once a week over a prolonged period. The aim of the study was through verbatim clinical material to bridge the gulf between some of the theoretic considerations of manic-depressive psychosis and the actual management and treatment of patients with this condition so that a more effectual adjustment to life could be made and further attacks prevented. The patient's ideas and emotions are presented under the headings: (1) self esteem; (2) love, including the need for love, as well as the capacity to give and receive love; (3) hate, with the patient's trend in both constructive and destructive aggression; (4) attitude toward body and mind; (5) anxiety and strength to bear it; (6) ambivalence; (7) tendency toward projection; (8) rigidity in thinking, and (9) identification, as well as something of how the patient handled a transference relation.

An important trend found in the personality makeup of patients who fell ill with this psychosis was a great need to be thought perfect in all spheres, such as physical attractiveness, intellectual capacity, wisdom and talent. One patient said, "If I am less than perfect, no one will want to have anything to do with me." Another said, "If I am not doing perfectly I am not doing well at all." These patients tended to use their own ideas of perfection and found it hard to take any behavior values from others. Their conscience and ego ideal were rigid, and they needed help in using a set of more tolerant values with their own.

Those manic-depressive patients who came into a treatment situation seemed to have great difficulty in expressing hostility. They could do this effectively when manic, or indirectly when depressed. Even in their normal interval they might express aggression within the family but had difficulty in being even normally aggressive with those outside the home or with the therapeutist. One said, "It takes more courage to hate some one else than to hate myself." Another said, "I would rather regard myself as weak and inadequate than blame another." This withholding of aggression, of course, impairs judgment and effectiveness in the everyday life of the manic-depressive person during his "well interval," and because of this weakness certain life situations get the best of him, until they can be solved only by a manic or depressive attack.

These manic-depressive personalities had great difficulty in dealing with love. Their apparent extrovertive friendliness hid great sensitivity. One said, "I can't tell you of the exuberance of having some one care about you or the despair of finding out that they do not." Another said, "When I am depressed I hurt so much all over that any one's friendship or love doesn't matter to me." As already stated, overtures of love cannot be accepted and utilized as readily by the manic-depressive personality as by the normal person, or even by the person with an average transference neurosis. This particular difficulty is one which only a favorable psychotherapeutic relationship can reach and help.

These manic-depressive persons had a great feeling of disgust for their own bodies, for the bodies of others and for body excretions. In this sphere, as well

as in the matter of self esteem, it seems much more difficult to get the manic-depressive patient to modify his opinions of himself than the patient with the ordinary transference neurosis. Like the patient with an obsessional neurosis, he is afraid of showing emotion. One patient said, "When I start feeling love I feel defenseless. I feel myself vulnerable to attack from people." Between attacks the manic-depressive person is not happy, even though he may often appear so.

Although it is too early to show the sustained results of psychotherapy, it is my opinion that prolonged and intensive treatment over a period of two years, more or less, would improve the functioning of the manic-depressive personality in such a way as to make the patient happier, more efficient, a better marital partner and less of a potential carrier of manic-depressive illness to offspring.

DISCUSSION

Dr. Theodore L. Dehne: For the most part I see patients with real psychoses and rarely have the opportunity to follow manic-depressive patients during the intervals of normal behavior; for that particular reason, Dr. English's presentation was most interesting and educational. Dr. English has definite advantages over a physician who sees only patients with acute illnesses. He sees the manic-depressive patient when he is well or convalescing, or perhaps the illness is just developing, and he can approach the problem slowly and painstakingly, with a great deal of study and care. In hospital practice one must approach the problem more directly and quickly, to get the patient over the period of hospitalization as rapidly as possible. Dr. English sees his patients when they are more or less accessible, but the manic-depressive patient who is ill enough to come to the hospital is, in my experience, almost completely inaccessible. I have no delusional ideas about the value of psychotherapy to a patient who is in the depth of a depression or at the height of a mania. However, hospitalization has much to offer to the patient in the way of good nursing care and removal from the environment that made him ill and from his family, the members of which are probably oversolicitous about him, fearful about him and often much annoyed by him. In hospital practice, one has a great advantage over the consulting psychiatrist in that one sees more patients in a given period than the latter is likely to see and sees the patient at the height of his illness. The more I study the manic-depressive personality, the more the conclusion is impressed on me that generalizations are dangerous. Any fixed notion about the structural concept of the disorder is likely to need a great deal of modification once one attempts to fit the patient's behavior and reactions into a strict structural concept. The picture is always a great deal more complicated than such a concept may permit one to believe.

The prepsychotic personalities of manic-depressive patients are as variable as those of any group one can imagine and cannot be classified under one head by any means whatever. Nor is the patient's hostility or his lack of it, or his aggressiveness or his lack of that, or the presence or absence of any other driving force an ever present factor.

In short, it is my opinion that variations in personality and behavior of manic-depressive patients are so wide that one can generalize about the illness only in a certain limited way.

Dr. Joseph C. Yaskin: As for the reactions of manic-depressive personalities between attacks, I am afraid I belong to that more rigid school which holds to the concept that the patient shows no lack of emotion between attacks. I wonder whether Dr. English did not have in mind the quality of emotion, rather than the quantity; whether he did not mean that, on the whole, the manic-depressive personality does not lack the necessary quantity of emotion, but that qualitatively it leaves something to be desired. Dr. English accurately described the helplessness and inability to accept help from others, as distinct from the depression occurring in the course of a psychoneurosis.

I should like to hear from Dr. English a little more about his success in preventing manic-depressive psychosis by treatment. I have gone so far as to

make no promises whatever any more. I have seen many persons lead a fairly happy existence, and with little or no provocation break out into an attack of depression or mania. Until the introduction of shock therapy I was not able to make a satisfactory prognosis—the attacks may last three and a half months to two years. How does Dr. English explain his psychoanalytic concepts in the light of the usefulness of shock therapy, which is so successful in the practical management of these patients?

DR. O. SPURGEON ENGLISH: I do not believe that Dr. Yaskin and I would disagree about the quantity of emotion between attacks, except that the manic-depressive person has difficulty in dealing with his emotions and the way in which they are bound together. He cannot say "no" when he should, and he cannot take a positive aggressive step when he should because of fear of being rebuffed.

As for results, I, naturally, cannot say how long these patients will stay well. I shall have to wait five, ten or twenty years to learn what the results will be. In the meantime I believe that the work done with these people has made them more effectual and has kept them living on a higher level, and working more satisfactorily.

What effect electric shock has on the manic-depressive psychosis I cannot say, although I should like to speculate about it. With electric shock there is undoubtedly loss of memory, and many of the patients would be glad to have some of their painful memories erased. I think electric shock does something to put farther from consciousness, to set aside in some way, the unpleasant complexes which keep the depression going on. Undoubtedly the pattern of ideas and their emotional charges are changed, but how I do not know, and I should not attempt to correlate it with what I have said.

Incest and Its Effect on the Participants. DR. PAUL SLOANE.

Since incest in the postadolescent period is not a common phenomenon among civilized people, it was interesting to come across 5 cases in one community within the space of five years. The cases reported were taken from the records of the Family Welfare Organization of Allentown, Pa. The reaction of the girl to the incest situation in each case was studied. The following conclusions seem to be justified as the result of the study. Indulgence in incest in the postadolescent period leads to serious repercussions in the girl, even in an environment in which the moral standards are relaxed. The offender, even though she may have been promiscuous with other men, reacts to incest as if it were socially condemnable and develops a good deal of guilt feeling toward her mother. This is probably related to the death wishes against the latter which are inherent in the incestuous relationship. The attempt to break away from incest leads to forcible types of reaction, the individual nature of which depends on the predisposition of the subject's personality and the relative strength of her ego and superego. In addition to the individual variations, however, one common manifestation appears to be a tendency to act out conflicts by indulging in promiscuous relationships instead of manifesting neurotic symptoms. This promiscuity increases the girl's feeling of guilt, so that she finally must give up even substitute forms of gratification or be prepared to endure ostracism from the fold. Only 1 of the 5 girls could be said to have worked out a satisfactory adjustment; the others showed various degrees of distortion of the personality. This is in contrast to the results found by Rasmussen and Bender and Balu in preadolescent children and can be explained by the increased strength of the superego in the postpubertal years. The destructive effects of incest seem to warrant the severity of the taboos which society has erected against it. (The full paper will appear in a forthcoming issue of the *American Journal of Orthopsychiatry.)*

DISCUSSION

DR. PHILIP Q. ROCHE: Dr. Sloane gives an instructive insight into the ego distortion that comes in his cases of incest. His presentation is devoted largely

to the effect of incest on the female. What effects are noted in male participants? It is my impression that there is a great deal more incest than would be currently indicated by the number of persons in prisons for such offense. Such offenders are almost invariably middle-aged or presenile first offenders who are more often protected by family silence than disposed of by the committing court. Investigation sometimes reveals that their prosecution is inspired less often by outraged morality than by motives of reprisal on the part of other members of the family group or out of interfamily conflicts. In such older offenders, one observes that their behavior is marked by awkwardness, lack of foresight, failure to efface traces and, peculiarly, by indifference after the offense. Incest is not uncommonly a harbinger of a psychotic reaction, which usually develops after imprisonment.

DR. MILTON K. MEYERS: It seems to me that attempts at incest are not rare. About a year ago statistics were compiled from questionnaires sent to women of all classes of society, and a surprising number said they had been attacked by members of their own families. I was astonished to learn that the practice was so common.

DR. O. SPURGEON ENGLISH: I fear that incestuous relations are of more common occurrence than is realized. I understand from social workers to whom I have talked that the father is not often sent to jail. It is difficult, apparently, for the community to take the word of the girl involved and to put the father in jail. One girl I know of has had much difficulty reestablishing good will with her family after she exposed her father. Another feels obliged to tell any man who becomes interested in her about her experiences, after which he has always become too "fresh" with her or has left her entirely. The social adjustment of the girl after being involved in incestuous relations is extremely difficult.

CHICAGO NEUROLOGICAL SOCIETY

ROY R. GRINKER, M.D., *President, in the Chair*

Regular Meeting, April 16, 1942

Experimental and Clinical Studies with Methylguanidine Sulfate. DR. JOHN J. MADDEN and DR. LEO A. KAPLAN.

This investigation included animal experimentation, studies on the chemical constituents of the blood and clinical observations on the use of methylguanidine sulfate with 52 mentally ill patients. As outlined in previous studies, methylguanidine sulfate is a nitrogenous metabolite related to creatinine which is regularly found in the blood stream and is excreted in quantities in the urine. In experimental animals it was determined that a shocklike physiologic change could be produced harmlessly by injecting certain concentrations of this chemical intravenously. It was further found that the untoward symptoms (convulsions, prostration, etc.) produced by injection of high concentrations could be promptly controlled by administration of calcium salts. A dose of 75 mg. per kilogram of body weight approached the upper limits of physiologic safety in dogs. With higher concentrations there occurred excessive restlessness, apprehension, respiratory irregularities, pronounced elevation of blood pressure and convulsive muscular movements. Adequate shocklike physiologic responses of less dramatic character took place when much lower concentrations were employed, and lower concentrations were therefore used in the clinical study.

The phenomena observed after injection into experimental animals may be summarized as follows: When methylguanidine sulfate was injected intravenously in doses of from 25 to 75 mg. per kilogram of body weight, an appreciable rise in blood pressure was observed. The elevation values were in direct relation to the concentration of the drug. The return to basal blood pressure was hastened

by injection of calcium gluconate, 10 to 20 cc. of a 5 per cent solution being used. Determinations showed a slowly progressing decrease of blood sugar, which approached the lowest level in the fourth hour and returned to approximately normal in the fifth hour.

In order to determine what pathologic changes might occur after administration of large doses over a comparatively long period, and also to study the acute pathologic changes when a massive lethal dose was given, several dogs were so treated. The pathologic changes were not significant.

In the clinical study, complete and detailed preliminary laboratory examinations and follow-up studies were made, consisting of an electrocardiogram, determination of the basal metabolic rate, and estimations of the nonprotein nitrogen, creatinine, calcium, phosphorus and sugar contents of the blood. An icteric index reading was made for 20 of the 52 patients, the available facilities precluding this study in every case; in this sampling of the group, no noteworthy deviations from normal were observed during or after the course of treatment.

The doses used with human subjects varied from 15 to 25 mg. per kilogram of body weight, 4 to 7 cc. of a 25 per cent solution of methylguanidine sulfate being injected intravenously. Injections were given five days a week for a series of approximately twenty treatments.

Of this group of 52 patients, 26, or 50 per cent, responded favorably. They were able to leave the hospital and return to their former environment and occupation free from overt symptoms. They may be considered as fully recovered at the date of this report. The mental illness of 43 patients was described as schizophrenia, or dementia praecox; of this group, 23, or 53 per cent, were considered improved. Four patients were classified as having cyclothymic depressions, 3 of whom were favorably influenced by treatment. Five patients whose symptoms were frankly psychoneurotic failed to show any noteworthy improvement.

Approximately 25 other patients were treated during this investigation, but because of factors beyond control, treatment was inadequate; the results in this group are not evaluated. No patient was under treatment more than four weeks, and not more than twenty injections were given in any case.

We believe that this therapeutic method is of definite value in the treatment of functional mental diseases, for the following reasons:

1. None of the disagreeable and dangerous features of the shock therapies is associated with this treatment; hence the therapy may be said to be a pharmacologic one, as opposed to the convulsive treatments or insulin shock.

2. The treatment is more agreeable to the patient; it is without danger, and cooperation from patient and relatives is more easily obtained.

3. The incidence of recovery is comparable to that obtained with shock therapies.

4. The duration of treatment was noticeably shorter than that of the average insulin treatment and was no longer than the period required by the more dangerous convulsive therapies.

5. The simplicity of administration and the cost are commendable features; the cost of the chemical for the therapeutic course is approximately $3.

6. This therapy is particularly suitable for office and home use, with no need for professional assistance.

DISCUSSION

DR. FRANCIS J. GERTY: The treatment introduced by Dr. Madden and Dr. Kaplan has not been used as widely as some of the more dramatic shock methods. Methods that are physically threatening to the patient seem to be in favor. Since experience has demonstrated that some pretty drastic things can be done with relative impunity, there seems to be an inclination to skirt the edge of danger. Persistence in the use of the less dramatic methods might give better results. Certainly, in some cases good results have been secured.

However, the matter which interests me chiefly is this: From the effects produced by intravenous injection of guanidine, may one not be justified in making

some guess as to the relation of oxygen consumption by the brain to the securing of therapeutic results? The easily observed effects of such an injection are flushing and increase in the pulse rate, blood pressure and respiratory rate. Hypoglycemia also is regularly produced. It is reasonable to suppose that immediately after the beginning of each treatment there is increased oxygen consumption and that for a succeeding period of several hours the utilization of oxygen is decreased. During the initial period the blood flow to the brain must be increased, in view of the effects of increased heart rate and blood pressure during a time in which there is dilatation of the arteries and increase in the respiratory rate, with presumable increase in the amount of tidal air. This would seem to indicate increased oxygen consumption by the brain. Experimental intravenous injections of sucrose and dextrose have been shown to increase the utilization of oxygen. Inasmuch as there is a decrease in blood sugar four or five hours after treatment with guanidine one might expect that there would be a compensatory decrease in utilization of oxygen by the brain during this period. It seems to me that more investigation on the oxygen–carbon dioxide relationship in the brain to all types of shock treatment is indicated and that such studies can best be undertaken with those types of shock therapy in which the assault on the organism is not so violent and extreme that adventitious side effects are produced.

DR. L. J. MEDUNA: There are two factors in this treatment which are remarkable, as Dr. Gerty has emphasized: the increase of blood pressure due to the injection and, at the same time, the decrease of blood sugar. The decrease of blood sugar indicates that the increase of blood pressure is not due to overproduction of epinephrine. If this were the case, one should see an increase of blood sugar at the time the blood pressure rises.

Ten or fifteen years ago methylenediguanidine, under the name of synthaline (decamethylenediguanidine), was recommended in the treatment of diabetes. I do not recall just why its use was discontinued. At any rate, there is at hand a drug which affects the carbohydrate metabolism of the body and brain. I believe that in treatments with continuous narcosis, in various convulsive treatments and in insulin shock the common denominator is the alteration of the carbohydrate metabolism of the brain. It seems that this action is present in the pharmacologic effect of the guanidine also.

Use of methylguanidine is a nonshock treatment. It would seem that the drug should be recommended first in treatment of any functional disease, and if, after a trial of four weeks, it does not bring about improvement, not much time has been lost for the inauguration of other, more drastic treatments.

DR. LEO A. KAPLAN: I should like to add to Dr. Meduna's discussion. Methylenediguanidine was used in Europe under the name of anticoman (a preparation containing pancreatic enzymes, sodium phosphate, tannic acid, bismuth subnitrate and decamethylenediguanidine tartrate) and in the United States as synthaline (decamethylenediguanidine) for the treatment of diabetes. Because it was necessary to use the drug over a long period, several cases of toxic hepatitis resulted, and its use was therefore discontinued. It was also found that calcium salts acted as a physiologic antagonist. In none of the cases was the damage to the liver permanent, and it was relieved by discontinuance of the guanidine and by administration of a calcium salt. In our work the dosage is less, and the period during which the drug is given is short.

With regard to Dr. Gerty's discussion, I should like to say that we did watch the retinal vessels during the injection of methylguanidine and found that they alternately dilated and contracted.

Neuropsychiatric Aspects of Aviation Medicine. DR. M. N. WALSH, Rochester, Minn.

The outstanding symptoms of altitude sickness belong in the domain of neuropsychiatry. A study of the behavior of human beings in low pressure chambers and in high-flying airplanes has demonstrated the fact that a decided individual variation exists with regard to the ability to withstand high altitudes. In general,

however, at an altitude of 6,000 to 9,000 feet (2,000 to 3,000 meters) various compensatory mechanisms involving the circulation and respiration are found. This altitude is known as the zone of reaction. Mental symptoms usually do not occur, although tense or psychoneurotic persons may have sudden syncope, which is not thought to have any relation to anoxemia. The next zone, at an altitude of from 12,000 to 15,000 feet (4,000 to 5,000 meters), is known as the zone of failing compensation. Mental symptoms occur at this altitude, the rapidity of their production depending on the man's susceptibility to altitude sickness, the degree of activity being carried out, the temperature and other factors. It is known that fatigue, alcohol, tobacco and the nervous tension of the flier may greatly influence his power of resistance to the deleterious effects of anoxemia. In this zone there occur a decrease in the acuteness of hearing and vision; blunting of judgment; impairment of critical perception; indolence of thought; forgetfulness and absent-mindedness; unmotivated changes in mood, such as euphoria or depression, and diminution or loss of the will to perform duties, even though tests may demonstrate that the ability to perform the duty is essentially unimpaired. It is important to note that the man himself is often unaware of the decrease in his own efficiency and will continue to feel that he is performing his duty satisfactorily. The great danger of any or all of the symptoms to an airplane pilot is evident.

The next zone is spoken of as the critical zone and lies between altitudes of 18,000 to 24,000 feet (6,000 to 8,000 meters). In this zone the symptoms previously noted in the zone of failing compensation are exacerbated. The patellar reflex increases in amplitude; muscular twitchings occur, followed by local and then general convulsive phenomena; amnesia and, finally, coma occur. The last zone is the lethal zone and is a function of the time when the critical zone is attained. All of the aforementioned reactions are reversible by administration of oxygen, if given in time, and before permanent and irreversible changes in the nerve cells occur.

The time reserve is defined as the period which elapses between the stoppage of an additional supply of oxygen, under conditions of extremely low atmospheric tension, for example, at an altitude up to 40,000 feet (12,000 meters), and the onset of threshold symptoms of failing compensation. This period is a matter of about thirty to sixty seconds at a height of 40,000 feet and of about fifteen seconds if activity is being carried out. Thus, in modern high altitude flying an uninterrupted supply of oxygen is a sine qua non in ail operations carried out at altitudes above 12,000 feet (4,000 meters), as the pilot who cannot maintain his efficiency at a high level is useless from a military standpoint.

A grave danger to the flyer who operates at high altitudes is the development of gas bubbles in his tissues, called by Armstrong "aeroembolism," or "the bends." This is due largely to the liberation of nitrogen by fatty or fibrous tissue. At an altitude of from 58,000 to 65,000 feet (17,500 to 19,800 meters) the blood "boils" and gas emboli occur. At lower altitudes gas escapes from the tissues and may be dangerous. It is not uncommon in high altitude or low pressure chamber work for acute pains to develop in or near joints, which on roentgenographic examination are found to be due to the accumulation of gas bubbles in the tissues. Armstrong demonstrated the production of gas bubbles in the spinal fluid of animals, and I have been able to show in human beings that at a simulated altitude of 12,000 feet in the low pressure chamber fine, champagne–like gas bubbles escape from the spinal fluid, and this continues for several minutes, up to a simulated altitude of 28,000 feet (8,500 meters). Roentgenograms of human and monkey heads at altitudes of 30,000 and 40,000 feet (10,000 and 12,000 meters) showed no free air in the ventricles of the brain. The breathing of pure oxygen with exercise before ascent will lessen the possibility of aeroembolism. There are on record cases of hemiparesis or hemiplegia, paraplegia and other grave accidents to the vascular supply of the brain under conditions of low atmospheric tensions, presumably due to gas emboli.

The effect of acceleration or rapid change of direction is much spoken of as "black-out." The centrifugal force produced in a cephalocaudal direction by steep

and tight turns and in pulling out of dives may produce cerebral anemia, or even the possibility of structural damage to the brain.

The unusual environment plus the great strain to which the flyer is exposed may produce a chronic fatigue state more rapidly than most other occupations. If the condition is continued, a neurosis may occur. Armstrong has described a special type of neurosis, the so-called aeroneurosis, as it affects experienced flyers. He defined it as a chronic functional disturbance characterized by gastric distress, nervous irritability, fatigue of the higher voluntary mental centers, insomnia and increased motor activity. It is important that a fatigue state be detected in its incipiency, since if it is allowed to progress to full development, a long period of rest must be taken, which means loss of the services of a highly trained flier for long periods, or even permanent incapacitation for flying. The rehabilitation of exhausted flying personnel is an activity of great importance, which must be carefully carried out for the best results. The flight surgeon lives with the fliers for the purpose of detecting fatigue states early and giving them prompt treatment. This may not be possible always under war conditions.

DISCUSSION

DR. PETER BASSOE: I do not know anything about aviation medicine, but I have had experience in the past with the effects of compressed air on caisson workers, and I ask myself whether there is not a difference between the phenomena as manifested by aviators and by divers. The man in the airplane starts with a balance of oxygen and nitrogen in his blood and then is subjected to lowering of the air pressure, which causes the nitrogen, being less absorbable, to escape into the tissues; the oxygen is more easily dissolved in the blood. As I see it, the difference lies in the fact that the caisson worker starts at a normal level, then is subjected to an abnormally high air pressure and gets a great deal of gas in solution in his blood; when he comes out too quickly, the nitrogen bubbles appear, and such phenomena as "bends" and "blind staggers" occur. Bubbles may accumulate so as actually to stop circulation at the auriculoventricular orifice. This I do not imagine could happen in aviators, for they never have such an overcharge of gas in the blood. I imagine that the anoxemia factor is greater in aviation while in caisson work the nitrogen factor is more important.

DR. L. J. POLLOCK: Will Dr. Walsh say something of the changes in water vapor in the body at high altitudes? Is that not one of the causes of bubble formation, in addition to release of nitrogen?

DR. MAURICE N. WALSH: Dr. Bassoe is correct in what he says about the difference between the disturbances in caisson workers and those in high altitude pilots. It is true that the pilot starts with normal conditions in his blood and does not have blood gases under pressure, as does the diver. However, I should say that the rapidity with which bubbles develop in the blood or tissues depends on the altitude attained and the rapidity of the climb. Human beings have rarely been exposed to extremely high altitudes; experimental animals, such as goats, have been brought up to 75,000 feet (30,000 meters). Bubbles are present in the cerebral circulation at that altitude. The problem of anoxemia is more important, however, for the air force. Some persons seem to be more susceptible to the effects of high altitude flying.

In reply to Dr. Pollock, the water vapor decreases with other components of atmosphere as one goes higher. So far as I know, the physiologic effect of this decrease has not been studied. Some of the effects which were thought to be due to anoxemia have been demonstrated to result from decrease in carbon dioxide. I believe there is much work to be done, and I regret that neuropsychiatrists have done little. A great deal of investigation has been carried out by physiologists and psychologists with little clinical experience. They have at times a rather biased attitude in trying to apply their observations, with disregard for the fact that human beings do not always conform to rules. I hope neuropsychiatrists in this country will take advantage of the opportunity which is offered.

Book Reviews

Sex Guidance in Family Life Education. By Frances Bruce Strain. Price, $2.25. Pp. 340. New York: The Macmillan Company, 1942.

This volume is evidence of a healthy trend in present day education. In the preface the author states that the book was written at the request of teachers the country over for a guide to sex education in the schools. Accordingly, it is written so as to offer a long range program, embracing all the grades from the primary to junior and senior high school, with the material arranged and adapted to the expanding sex interest of children from the early years to adolescence.

Throughout the book the author emphasizes both the biologic and the psychobiologic aspects of sexual development and is as much concerned with the dynamics of social and emotional growth as with reproduction. Many practical suggestions are outlined in chapters devoted to methods of gaining community support, matters of organization, family relations, and technics in sex teaching. Special chapters are devoted to the organization of sex guidance counseling centers and the personal and academic qualifications of the counselor.

The book is full of good observations and sensible suggestions. Mrs. Strain says that just as sociologists are able to plot delinquent areas in a city through the presence of delinquency-producing factors, so the sex education worker can plot areas of pornography, for they are found where the public attitude, talk and behavior present the sex life as degraded and degrading. Her experience leads her to state that "constructive sex teaching leads invariably toward the lessening of objectionable activities in school or community."

As would be expected, much of the volume is devoted to child guidance and mental hygiene. In the field of sex education the happy cooperation of the teacher, the biologist, the child psychologist, and the psychiatrist is necessary. Mrs. Strain has indicated a good road in this direction. This book is highly recommended and should be read by all teachers. It is also well worth the attention and interest of the psychiatrist.

Visual Mechanisms. Edited by H. Klüver. Volume VII of Biological Symposia, Jaques Cattell, editor. Price $3.25. Pp. 322. Lancaster, Pa.: Jaques Cattell Press, 1942.

This collection of papers is an extension of those presented at one of several symposiums on "New Frontiers in Education and Research," held in celebration of the fiftieth anniversary of the University of Chicago, in 1941. In it problems of vision are considered from the physical, biochemical, physiologic, anatomic and psychologic points of view. Each author presents and integrates the material from a series of contributions, the individual study of which would be quite impossible for any one but a specialist in the field. The appearance of such a collection at the present time is particularly opportune in that it provides a base from which investigation can be resumed should its progress falter in these troubled times. For the general reader who desires to acquaint himself with the most recent developments in these varied aspects of vision, as well as for the neurologist who is employing electrophysiologic methods in diagnosis, the individual contributors, Dr. Klüver as editor and the Jaques Cattell Press as publishers have performed a signal service.